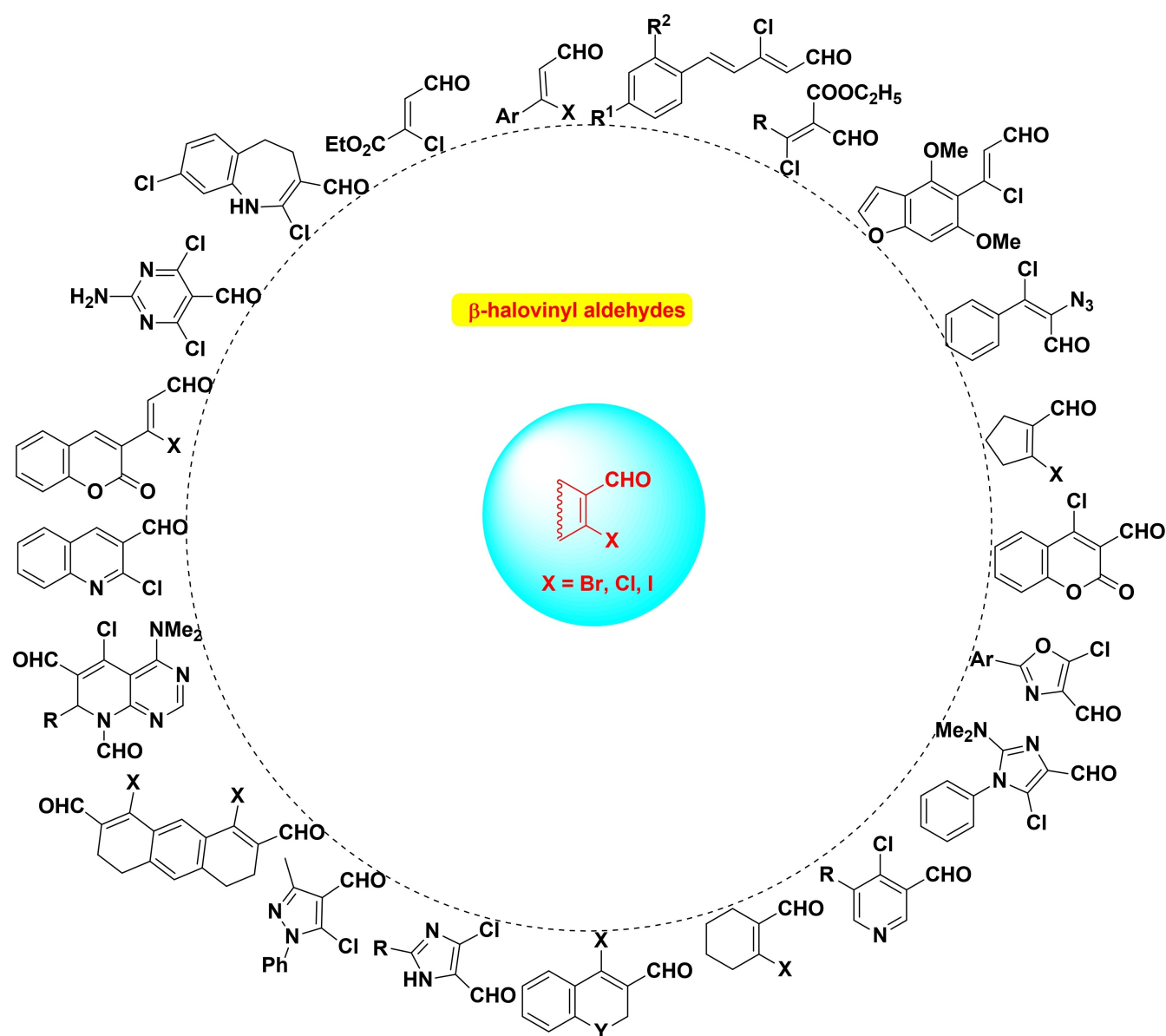


β -halovinyl Aldehydes: Multifaceted Versatile Building Blocks In Organic Synthesis

Paras Saini,^[a] Jyoti,^[a] Pawan K. Sharma,^{*,[b]} and Virender Singh^{*,[a]}

This article is dedicated to Prof. Jayanta K. Ray for seminal contribution to β -halovinyl aldehydes.



β -halovinyl aldehydes serve as a valuable building blocks in organic synthesis. These aldo-x bifunctional building blocks (AXB3s) contain an alkenic double bond (vinyl) as well as a formyl group along with a halogen atom (Cl, Br, I) bonded with the β -carbon atom of vinyl aldehyde. Owing to the presence of these multiple reactive sites, β -halovinyl aldehydes act as a suitable precursor for Michael addition, direct addition, addition-elimination reactions, cross-coupling reactions, condensation reactions, nucleophilic substitution reactions, domino reactions,

MCRs, Diels-Alder reaction, functional group transformation reactions and enantioselective transformations. Therefore, a comprehensive review on synthetic exploration of β -halovinyl aldehydes has been carried out for the generation of reactive intermediates and diverse bioactive heterocycles by using various C–C, C–N, C–S and C–O bond forming reactions. In this review, we have assembled the literature from mid-2007 to Jan 2024.

1. Introduction

Vilsmeier-Haack reaction is an organic reaction that is frequently used for the formylation of keto methylene compounds as well as electron rich aromatic moieties by using DMF and $\text{POCl}_3/\text{PBr}_3$.^[1] Interestingly, Vilsmeier-Haack reaction of keto methylene compounds result in formylation as well as chlorination leading to the formation of β -halovinyl aldehydes.^[2] These aldehydes are also known as β -halo acroleins as well as β -halo acrylaldehydes belonging to a class of compounds that are of keen interest to chemists in organic synthesis owing to their versatile reactivity. These substrates contain an alkenic double bond (vinyl) as well as a formyl group along with a halogen atom (Cl, Br, I) bonded with the β -carbon atom of vinyl aldehyde. Owing to the presence of these multiple reactive sites, β -halovinyl aldehydes serve as valuable building blocks in organic synthesis for Michael addition, direct addition, cross-coupling reactions, condensation reactions, nucleophilic substitution reactions, Diels-Alder reaction, functional group transformation reactions and enantioselective transformations.^[3] Being α,β -unsaturated aldehydes, they function as the versatile Michael acceptors and reacts with different C, N, O, S- nucleophiles like amines, enolates, thiols, active methylene compounds etc. More appropriately, they react through addition-elimination sequence. The halogen moiety present at the vinylic or benzylic position readily engages in different cross-coupling reactions such as Suzuki, Heck, Sonogashira, Stille, and Buchwald-Hartwig which result in the formation of both carbon-carbon or carbon-heteroatom bonds as reviewed by Ray group.^[4] Furthermore, the halogen moiety at β -position also readily undergoes functionalization through nucleophilic substitution reactions and sometimes its reactivity dominates the formyl functionality depending on the reaction conditions. It is mentioned that there is no specific report on the relative reactivity of β -chloro/ β -bromo/ β -iodo-vinyl aldehydes. However, It has been observed that base-mediated simple nucleophilic substitution reactions proceed faster in chloro-vinyl aldehydes than bromo-vinyl aldehydes. While transition metal catalyzed reactions like

Sonogashira/Heck coupling proceed faster and with better yields in bromovinyl aldehydes than chlorovinyl aldehydes. As the multiple reactive sites are present in β -halovinyl aldehydes, they tend to be attractive substrate for cascade cyclisation reactions with bifunctional substrates to generate diverse heterocycles as well as carbocycles. β -halovinyl aldehydes can undergo asymmetric synthesis, facilitating the formation of chiral molecules having high stereoselectivity by using appropriate chiral catalysts.

β -halovinyl aldehydes are commonly synthesized by using Vilsmeier-Haack reagent ($\text{POCl}_3 + \text{DMF}$) since its discovery in 1927.^[5] Arnold and Zemlicka were the first to carry out the reaction of keto methylene compound with $\text{POCl}_3 + \text{DMF}$ in 1958 to get β -chlorovinyl aldehydes whereas the bromo analogues of Vilsmeier-Haack reaction were reported in 1961.^[6] Over the past years, β -halovinyl aldehydes have attracted much attention of researchers owing to their ability to deliver pharmacologically potential scaffolds with antimicrobial, anti-malarial, anti-fungal, anti-inflammatory, antimycotic, antiviral and analgesic activities. β -halovinyl (mainly chloro- or bromo-vinyl) aldehydes are most commonly employed to synthesize various mono-, bi-, poly-cyclic and spiro heterocycles which play an important role in medicinal chemistry, biochemistry, and material science. Pharmaceuticals and agrochemicals are the main applications of the heterocyclic compounds afforded from β -halovinyl aldehydes.^[7]

2. Mechanism and Synthesis of β -halovinyl Aldehydes

β -halovinyl aldehydes are of keen interest to organic chemists due to the presence of multiple reactive sites; therefore, a few previous reports have appeared in literature to fuel up the exploration of these building blocks.^[4,8] Accordingly, in this review, we have assembled literature on synthetic utility of acyclic β -halovinyl aldehydes from mid 2007 to mid 2024.^[8] Synthesis of various kinds of β -halovinyl aldehydes has been summarized in Table 1. Arnold *et al.* (1958) succeeded to carry out the reaction of keto methylene compounds with DMF and POCl_3 for the first time and the following mechanism has been proposed for the formation of β -chlorovinyl aldehydes **6** as depicted in Figure 1. It was proposed that DMF reacts with the POCl_3 to form chloro iminium salt (**1**, N-(chloromethylene)-N-methylmethanaminium) known as the "Vilsmeier reagent". Then

[a] P. Saini, Jyoti, V. Singh
Department of Chemistry, Central University of Punjab, Bathinda, Punjab 151401, India
E-mail: virender.singh@cup.edu.in

[b] P. K. Sharma
Department of Chemistry, Central University of Haryana, Jant-Pali, Mahendergarh, Haryana 123031, India
E-mail: talk2pawan@gmail.com

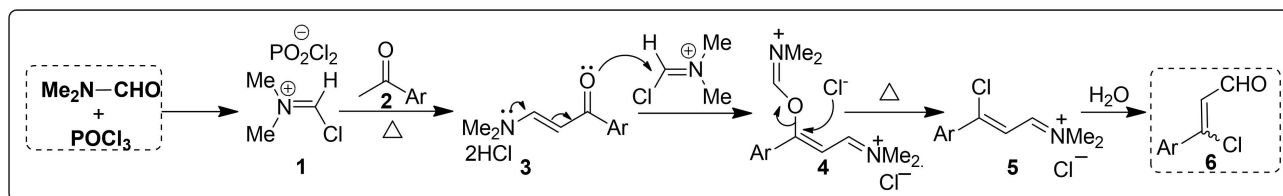


Figure 1. Mechanism for the formation of β -chlorovinyl aldehydes.

electron rich methylene ketone **2** attacks the chloroiminium ion **1** resulting in the formation of enamine intermediate **3** which further undergoes delocalization of electrons and reacts with 2nd equivalents of chloroiminium ion **1** to furnish the intermediate **4**. The intermediate **4** upon nucleophilic attack by *in situ* generated chloride ion results in formation of **5** which upon hydrolysis generates the β -chlorovinyl aldehydes **6**.

2.1 Mechanism for the Formation of β -bromovinyl Aldehydes

Furthermore, Arnold and Holy (1961) generated the bromo analogue of Vilsmeier-Haack reaction and the proposed mechanism has been depicted in Figure 2.

By using these procedures, a variety of β -halovinyl aldehydes have been synthesized with alkyl, aryl as well as heteroaryl substituents. Importantly, some of the β -halovinyl aldehydes contain an important heterocyclic pharmacophore



Paras Saini was born in Roorkee Uttarakhand, India in 2002. He received his Bachelor's degree in 2022, from Hemvati Nandan Bahuguna University, India. He completed his M.Sc. in Chemistry in 2024 at Central University of Punjab, India. His research interests include synthetic applications of β -halovinyl aldehydes.



Ms Jyoti completed her graduation and Post-graduation from Maharishi Dyanand University, Rohtak, Haryana, India. In 2022, she joined Prof. Virender Singh's group as a doctoral fellow in the Department of Chemistry, Central University of Punjab, Bathinda, India. Her research interests involve exploration of synthetic potential of β -halovinyl aldehydes for the development of bioactive aza-heterocyclic scaffolds.



Pawan K. Sharma is Professor of Chemistry at Central University of Haryana, Mahendergarh. He received his Ph.D. degree from Kurukshetra University (KU) and after a brief stint at Lupin Laboratories, he joined KU as Lecturer (1996) where he worked till May 2023 as Professor of Chemistry. He conducted post-doctoral research at the University of Iowa, USA (1998–2000) and later worked in Antarctica as a member of the Indian Scientific Expedition team (2002). He was Research Associate Professor (2003–2005) at the Nucleic Acid Center, University of Southern Denmark (SDU), and has been a regular visiting researcher to SDU for over a decade. He has published over 140 original research papers and is the joint holder of five granted patents. His research interests include synthetic applications of β -halovinyl aldehydes.



Prof. Virender Singh has done his graduation and Post-Graduation in chemistry from Kurukshetra University, Haryana, India. He completed his Ph D from CSIR-Central Drug Research Institute (CDRI) Lucknow in 2011 in the area of synthetic organic and medicinal chemistry with Dr Sanjay Batra. After PhD in 2011, he joined Central University of Punjab as Assistant Professor. In 2012, he moved to Dr B R Ambedkar National Institute of Technology (NIT) Jalandhar as Assistant Professor in Chemistry. After 8 years at NIT Jalandhar, he moved back to Central University of Punjab as Associate Professor in 2020. Currently, he is working as full Professor in Chemistry since 2023. His area of research interests includes the development of novel methodologies via exploration of aldo-x bifunctional building blocks. He has been the recipient of several awards like Sh. NandLal Telesara Memorial Award, Prof. S.M. Mukherji Award for excellence in Chemistry, Prof. C.P. Garg Medal, Lupin Award, Young Scientist award and Dr. M.M. Dhar Memorial Award from CDRI, Lucknow for his academic and research contributions.

Table 1. Summary of synthesis of various β -halovinyl aldehydes.

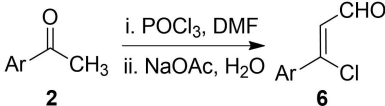
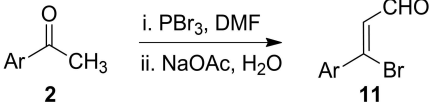
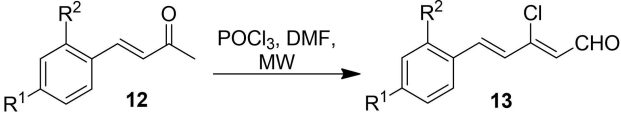
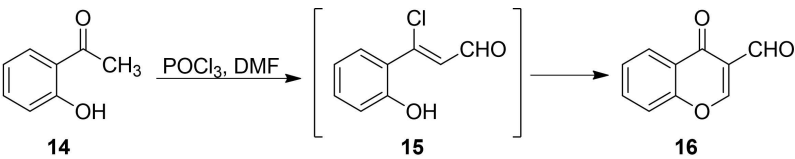
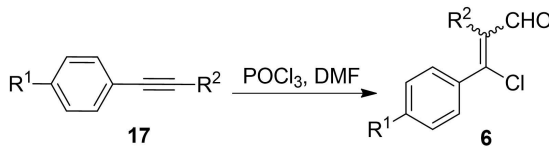
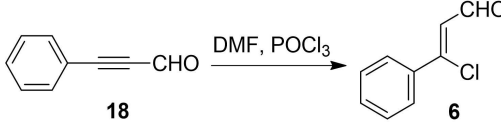
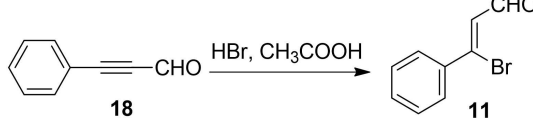
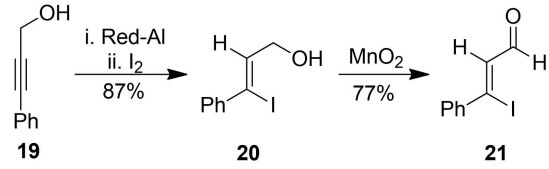
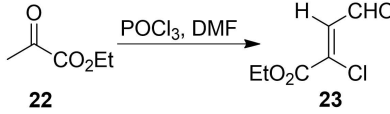
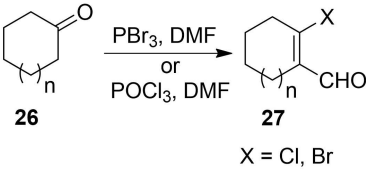
Sr. No.	Reaction conditions	Reference
1.		[9]
2.		[10]
3.		[11]
4.		[12]
5.		[13]
6.		[14]
7.		[15]
8.		[16]
9.		[17]
10.		[18]
11.		[19]

Table 1. continued		
Sr. No.	Reaction conditions	Reference
12.		[20]
13.		[21]
14.		[20]
15.		[20]
16.		[22]
17.		[23]
18.		[23]
19.		[24]
20.		[25]
21.		[26]

Table 1. continued

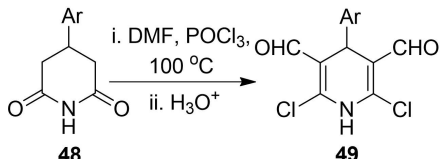
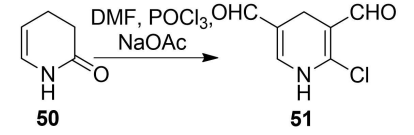
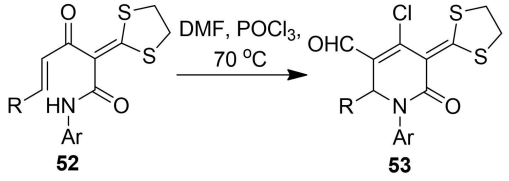
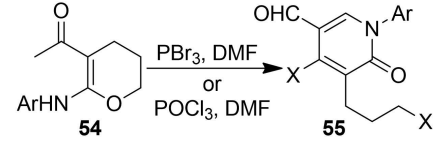
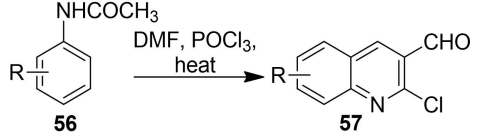
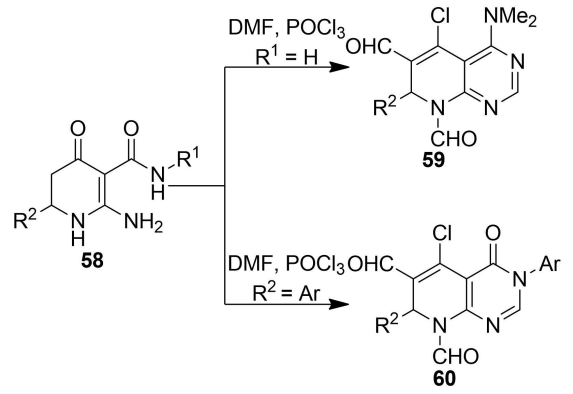
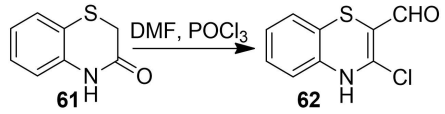
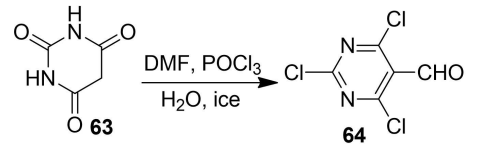
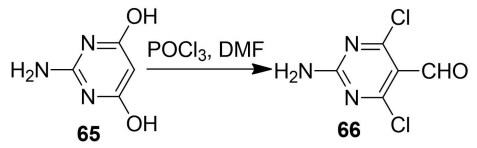
Sr. No.	Reaction conditions	Reference
22.	 48 $\xrightarrow[\text{ii. H}_3\text{O}^+]{\text{i. DMF, POCl}_3, 100\text{ }^\circ\text{C}}$ 49	[27]
23.	 50 $\xrightarrow{\text{DMF, POCl}_3, \text{NaOAc}}$ 51	[27]
24.	 52 $\xrightarrow{70\text{ }^\circ\text{C, DMF, POCl}_3}$ 53	[28]
25.	 54 $\xrightarrow[\text{or POCl}_3, \text{DMF}]{\text{PBr}_3, \text{DMF}}$ 55	[29]
26.	 56 $\xrightarrow[\text{heat}]{\text{DMF, POCl}_3}$ 57	[30]
27.	 58 $\xrightarrow[\text{DMF, POCl}_3, \text{R}^2 = \text{Ar}]{\text{DMF, POCl}_3, \text{R}^1 = \text{H}}$ 59 58 $\xrightarrow[\text{DMF, POCl}_3, \text{R}^2 = \text{Ar}]{\text{DMF, POCl}_3, \text{R}^1 = \text{H}}$ 60	[31]
28.	 61 $\xrightarrow{\text{DMF, POCl}_3}$ 62	[32]
29.	 63 $\xrightarrow[\text{H}_2\text{O, ice}]{\text{DMF, POCl}_3}$ 64	[33]
30.	 65 $\xrightarrow{\text{POCl}_3, \text{DMF}}$ 66	[34]

Table 1. continued		
Sr. No.	Reaction conditions	Reference
31.		[35]
32.		[36]
33.		[32]
34.		[37]
35.		[38]

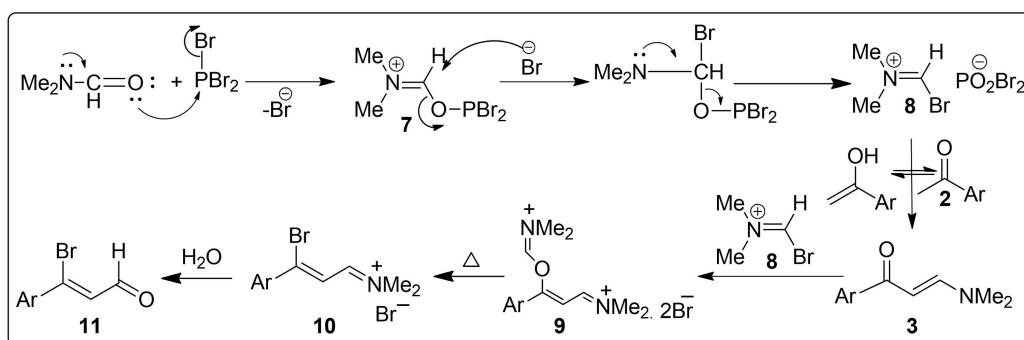


Figure 2. Mechanism for the formation of β -bromovinyl aldehydes.

such as coumarin, imidazole, pyrrole, pyridine, pyrimidine, indole, benzofuran, oxazole, quinoline, benzoazepine, benzo-thiazine, imidazopyridine etc. as summarized in Table 1.

2.2. Overview of the Heterocycles Synthesized Till Mid-2007

Since the discovery of β -halovinyl aldehydes, many research groups have carried out different reactions on β -halovinyl aldehydes and prepared different biologically active compounds. An overview of the different heterocycles generated from β -halovinyl aldehydes upto 2007 are depicted in Figure 3.^[39]

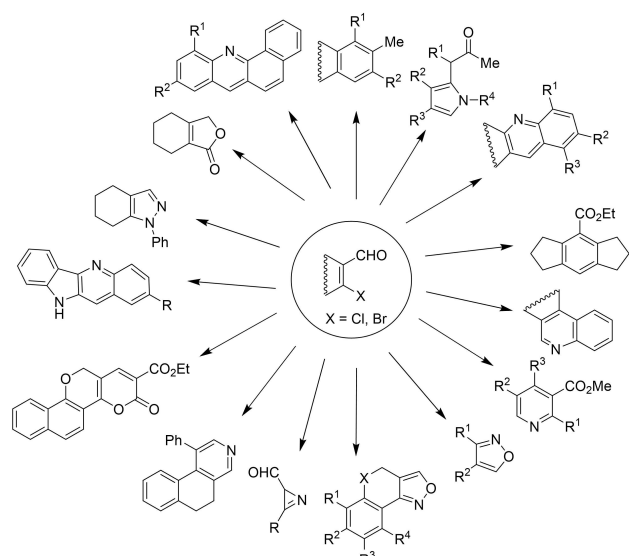


Figure 3. An overview of the different heterocycles generated from β -halovinyl aldehydes upto 2007.

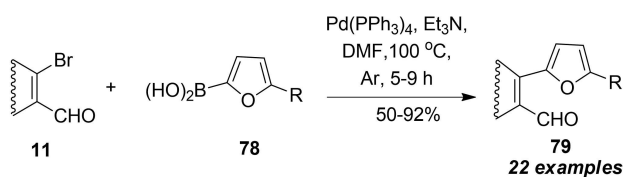
3. Reactions and Functionalisation of β -halovinyl Aldehydes

The functionalisation of β -halovinyl aldehydes have been achieved through various chemoselective reactions at halogen and/or formyl group. While in some cases, substitution as well as condensation or addition reactions take place simultaneously at halogen and formyl group while some multifunctional substrates trigger cascade reaction leading to aromatic heterocycles. In addition to this, some functional group transformations reactions have also been reported with β -halovinyl aldehydes to convert them into other reactive building blocks.

3.1. Pd-catalysed Functionalisation of β -halovinyl Aldehydes Through Reaction at Halogen Atom

Sarkar group carried out the functionalisation of β -halovinyl aldehydes and developed a general methodology for the synthesis of β -(2-furyl)-acroleins **79** via Suzuki coupling of furan-2-boronic acids **78** with β -bromovinyl aldehydes **11** (Scheme 1).^[40]

Singha *et al.* transformed β -bromovinyl aldehydes **11** into β -bromovinyl carboxylic acids **80** and succeeded to develop an efficient protocol for 1,3-diynes **81** which is another versatile

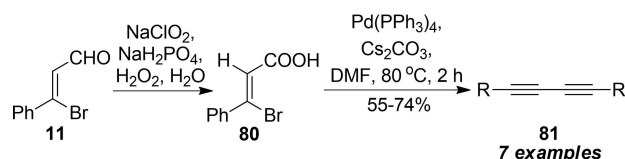


Scheme 1. Pd-catalyzed Suzuki coupling for the synthesis of β -(2-furyl)-acroleins.

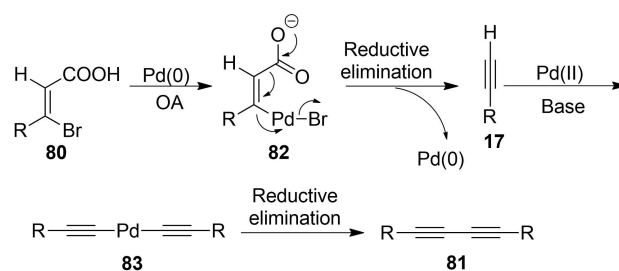
building block in organic synthesis.^[41] Under Pd-catalyzed conditions, β -bromovinyl carboxylic acids **80** decomposed like 2-diazoniumbenzoic acid to generate the benzyne like intermediates. First a terminal alkyne **17** was generated via the Pd-catalyzed decomposition of β -bromovinyl carboxylic acid **80**. Furthermore, terminal alkynes underwent dimerisation to furnish the 1,3-diynes **81** under the influence of palladium catalyst (Scheme 2). A probable mechanism for the formation of 1,3-diynes **81** has been depicted in Scheme 3.

Mathur and co-workers developed a selenated NHC-Pd(II) full pincer complex catalyst **86** and carried out the Suzuki-Miyaura coupling between (2-formyl-1-chlorovinyl)ferrocenes **84** and aryl-boronic acids **85** using this Pd-catalyst.^[42] Interesting, Suzuki-Miyaura coupling took place in water under normal atmospheric conditions to furnish the functionalized ferrocene derivatives **87** (Scheme 4). Some interesting facts came into notice after the Solvatochromic studies of synthesized ferrocene derivatives. An increase of the absorbance with decrease in amount of water and DMSO was recorded after aggregation studies. A mechanistic path for the Suzuki-Miyaura coupling is shown in Scheme 5.

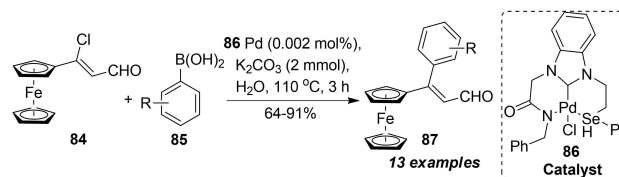
Joshi group recently demonstrated another catalytic application of this NHC-Pd(II) full pincer complex catalyst **86** and developed an efficient route for the synthesis of ferrocenated enynes **91** by reaction of ferrocene substituted β -chloro acrylaldehydes **84** with terminal alkynes **17** via Sonogashira cross-coupling reaction under copper-free and aerobic conditions (Scheme 6).^[43] They examined that 0.002 mol % of



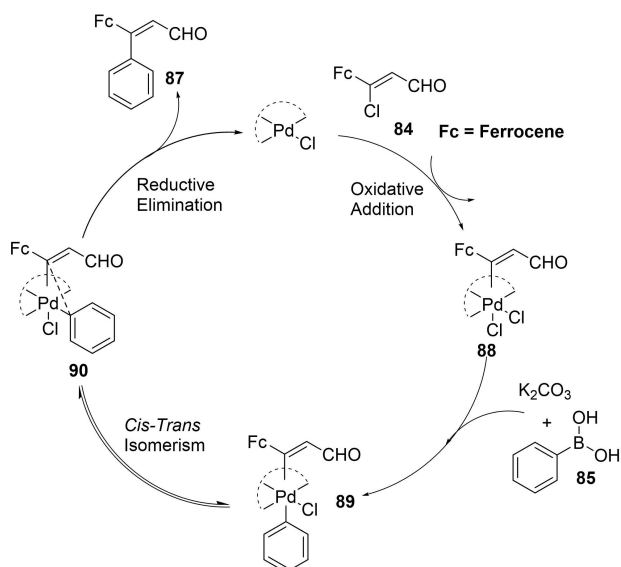
Scheme 2. Pd-catalyzed synthesis of 1,3-diynes.



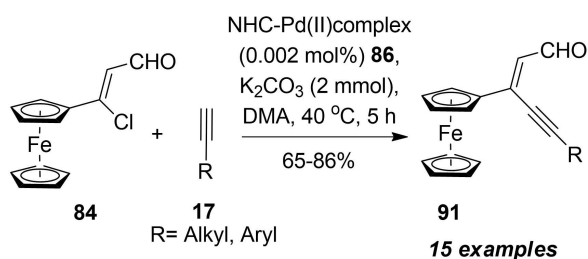
Scheme 3. Mechanistic cycle for the formation of 1,3-diynes.



Scheme 4. Synthesis of ferrocenated enynes via Suzuki-Miyaura coupling reaction.



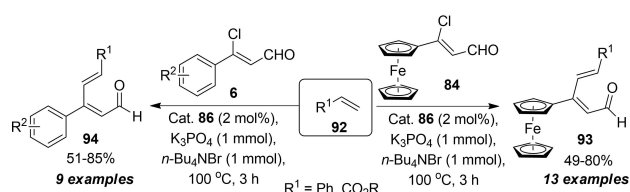
Scheme 5. Probable reaction mechanism for Suzuki-Miyaura coupling of (2-formyl-1-chlorovinyl)ferrocenes.



Scheme 6. Synthesis of ferrocenated enynes *via* Sonogashira cross coupling reaction.

catalyst was more than enough for the coupling reaction under the aerobic conditions within 5 hours and synthesized a library of 15 ferrocene substituted enynes **91** using this strategy. They also investigated the electrochemical responses of the generated products **91**.

In an extension to their previous findings, this group also established a method to synthesize new ferrocenylated conjugated diene derivatives **93** by reacting (2-formyl-1-chlorovinyl) ferrocenes **84** with vinyl arenes and acrylates **92** *via* Heck reaction under solvent free conditions using selenated NHC-Pd(II) full pincer complex as a catalyst **86** (Scheme 7).^[44] It was found that this complex was extremely effective and highly stable at high temperature and executed the Heck coupling within 3 hours under inert and solvent-free conditions. It was

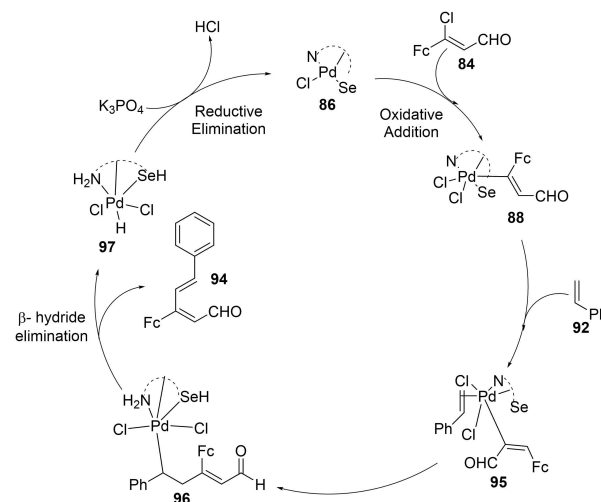


Scheme 7. Synthesis of conjugated dienes *via* Heck coupling.

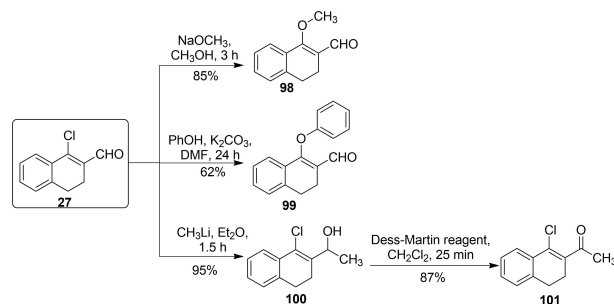
found that the catalyst **86** was equally efficient for the Heck coupling of β -chloro acrylaldehydes **6**. Furthermore, it was noticed that the reaction exhibited high tolerance for almost all functional groups and delivered remarkable results with all variants of styrene and acrylates (Scheme 8).

3.2. Functionalisation of β -halovinyl Aldehydes Through Nucleophilic Substitution Reaction at Halogen

It has been observed that β -halovinyl aldehydes preferably undergoes nucleophilic substitution reaction at halogen with various oxa- and aza- nucleophiles instead of condensation with formyl group. It is anticipated that nucleophilic substitution reaction occurs via addition elimination mechanism as β -halovinyl aldehydes act as excellent Michael acceptor favouring 1,4-addition while being benzylic carbon it finally leads to elimination of β -halogen resulting in overall preferred nucleophilic substitution reaction in β -halovinyl aldehydes. In this respect, Katzenellenbogen group carried out the functionalization of cyclic β -chlorovinyl aldehydes **27** *via* nucleophilic substitution reaction with oxa-nucleophiles; alkoxides and phenoxides resulting in formation of β -functionalised vinyl aldehydes **98–99** (Scheme 9).^[45] These precursors were further utilized for the synthesis of a series of guanyldrazones that



Scheme 8. Plausible mechanism for Heck reaction.



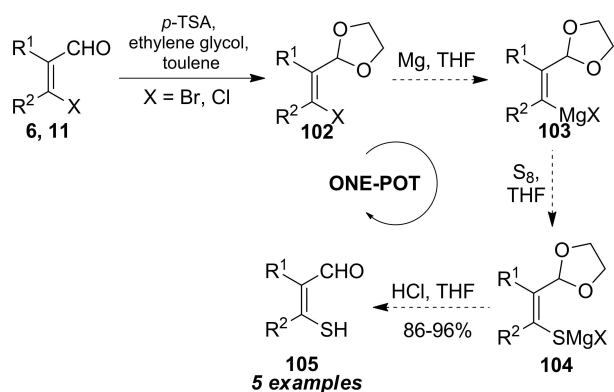
Scheme 9. Functionalisation of β -chlorovinyl aldehydes with oxa-nucleophiles.

were designed to block estrogen receptor (ER) activity. It was also found that reaction with organolithium reagent (MeLi) resulted in 1,2-addition reaction and successive oxidation of alcohol **100** yielded the β -chlorovinyl ketone **101**.

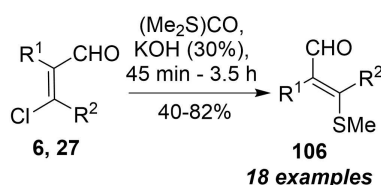
Xiaoyan group developed a novel one-pot strategy to synthesize β -mercapto acrylaldehydes and 2-mercaptocyclohex-1-ene carboxaldehydes **105** using β -chlorovinyl aldehydes **6**, **11** as the precursors. Reaction proceeded *via* the protection of formyl group followed by *in situ* generation of Grignard reagent **103** and then reacting with elemental sulfur to yield the acetal derivatives **104** and successive demasking of acetal with HCl afforded the β -mercaptoacrylaldehydes **105** in excellent yields (Scheme 10).^[46]

Junjappa and co-workers found that dimethyldithiocarbonate (DDC) and 30% aq. KOH may be used as a great source of methylthiolate anion and made use of this reagent to develop an efficient methodology for the synthesis of novel β -aryl- β -(methylthio)acrylaldehydes **106** using 1,3-dielectrophilic synths, β -chloroacrylaldehydes **6**, **27** (Scheme 11).^[47] It was revealed that the synthesis can take place *via* a one-pot strategy or can be carried out in two steps.

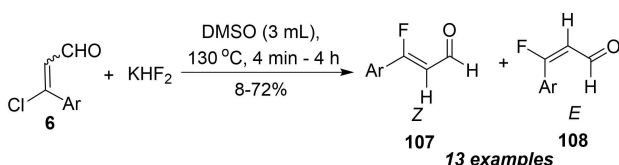
Controlling the *Z/E* stereoselectivity in multi substituted monofluoroalkene products in one-pot strategy still remained as a challenging task. Keeping this problem in view, Gong and



Scheme 10. Synthesis of β -mercaptoacrylaldehydes.



Scheme 11. Synthesis of β -(methylthio)acroleins.



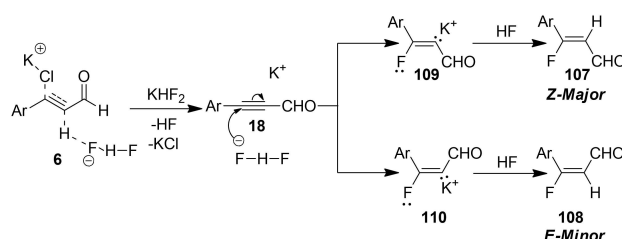
Scheme 12. Synthesis of (*Z*)- β -monofluoro tri-substituted alkenes.

co-workers realised a remarkable one-pot regio- and stereo-selective strategy for preparing functionalized (*Z*)- β -monofluoro tri-substituted alkene derivatives **107–108** by using easily accessible β -chlorovinyl aldehydes **6** (Scheme 12).^[48] It was proposed that KHF₂-assisted dehydrochlorination of β -chlorovinyl aldehydes **6** produced alkynyl aldehydes **18** as intermediate, which then resulted in *trans*-hydrofluorination (Scheme 13). It was found that fluorinating reagent having desirable basic and nucleophilic character played a vital role for enhancing the selective generation of (*Z*)- β -fluoro- β -aryl tri-substituted monofluoroalkene derivatives.

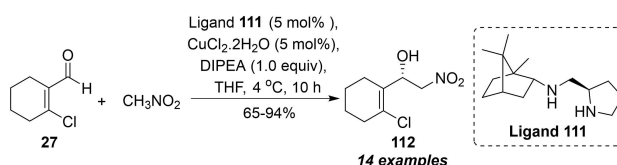
3.3. Functionalisation of β -halovinyl Aldehydes Through Reaction at Formyl Group

Previous findings have revealed that reaction at formyl group in β -halovinyl aldehydes is favoured under acidic conditions in presence of Lewis or Bronsted acid. The nucleophilicity of reagent as well as neutral and mild basic conditions were also found to favor the reaction at formyl group. In this direction, an effective method for carrying out extremely chemo- and enantio-selective nitro-aldol reaction (Henry reaction) to yield chiral functionalized allylic alcohols **112** (up to 94% yield and 99% ee) having halogen as well as nitro groups was generated by Gong group by reacting β -halovinyl aldehydes **27** with nitromethane under mild conditions in presence of L-proline based ligand **111** and Cu(II) catalyst (Scheme 14).^[49]

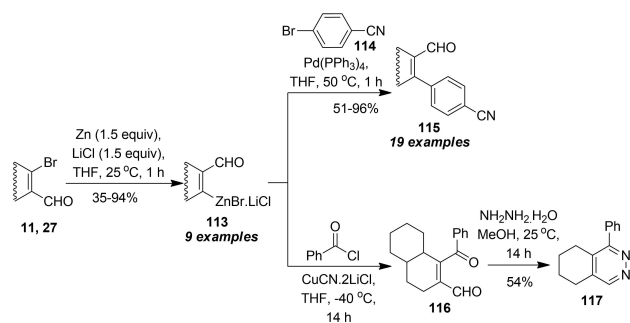
Knochel and co-workers succeeded to carry out the direct insertion of Zn/Mg into β -halovinyl aldehydes **11**, **27** in presence of LiCl to prepare the cyclic and acyclic alkenylzinc reagents **113** having diverse functionalities like aldehyde, ketone, esters etc (Scheme 15). These alkenylzinc reagents **113** were found to suitable reactive intermediate to execute the Negishi cross-coupling, acylation, and allylation reactions and provided the poly-functional compounds and aza-heterocycles **115–117** in very good yields.^[50]



Scheme 13. Proposed mechanism for the formation of (*Z*)- β -monofluoro tri-substituted alkenes.



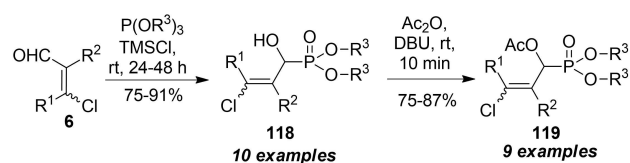
Scheme 14. Synthesis of chiral nitro allylic alcohols *via* Henry reaction.



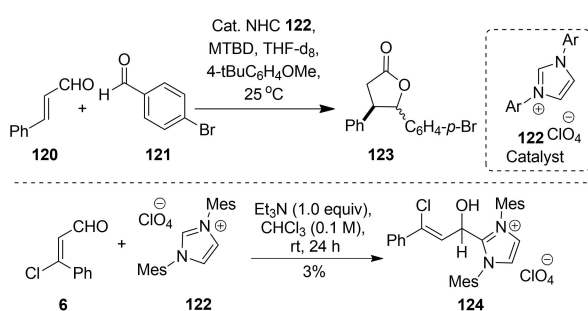
Scheme 15. Synthesis of alkenylzinc reagents and cross-coupling reactions.

α -hydroxyphosphonates **118** were prepared by Baccari and co-workers by reacting β -halovinyl aldehydes **6** and trialkyl phosphates under solvent free conditions at room temperature in the presence of chlorotrimethylsilane in 75–91% yields. α -hydroxyphosphonates **118** further reacted with acetic anhydride in DBU to furnish the new α -acetoxyphosphonates **119** (Scheme 16)^[51] as a mixture of *E* and *Z* isomers of phosphonates.

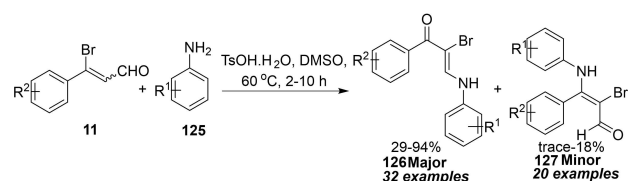
Narumi and co-workers developed a NHC based catalyst **122** which upon reaction with α,β -unsaturated aldehydes **120** and aryl aldehyde **121** afforded the γ -butyrolactones (Scheme 17). Surprisingly, this imidazolylidene catalysts yielded



Scheme 16. Synthesis of α -hydroxyphosphonates and α -acetoxyphosphonates.



Scheme 17. Isolation of IMes- α,β -enal adduct.



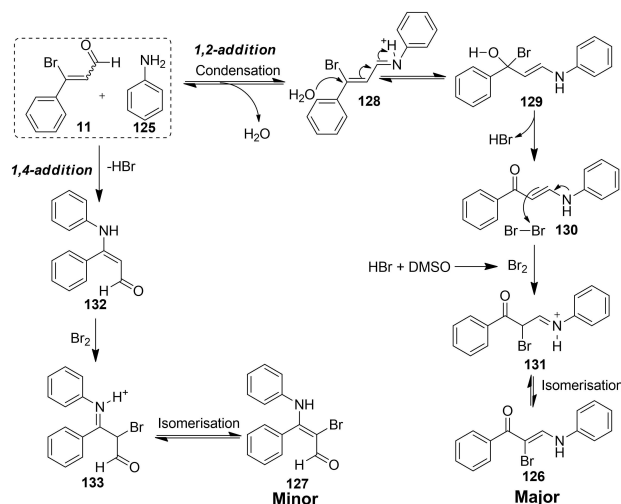
Scheme 18. *p*-TsOH.H₂O catalyzed synthesis of α -functionalized enaminones.

the isolable IMes- α,β -enal adduct **124** upon similar reaction with β -halovinyl aldehydes **6**.^[52]

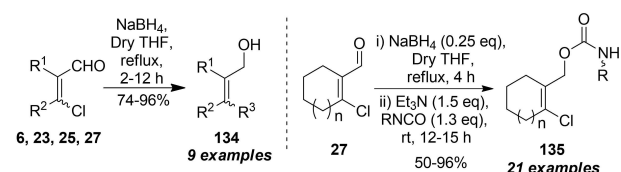
Yao group discovered a one-pot strategy to synthesize α -bromo enaminones **126–127** via reaction of β -bromovinyl aldehydes **11** with anilines **125** (Scheme 18). Interestingly, *p*-TsOH.H₂O catalyzed reaction of β -halovinyl aldehydes **11** with anilines **125** in DMSO followed two different routes and did not demand any external brominating agent. By making use of aniline with a sterically hindered electron accepting group present at the *o*-position, the chemoselective 1,2-addition was favoured. While the reactions with other anilines as the nucleophiles produced the 1,4-addition product in minor or poor yields. β -halovinyl aldehydes demonstrated a distinct range of reactivity with various kind of anilines as represented in Scheme 19.^[53]

Slimi and co-workers reported a one-pot strategy for the synthesis of novel γ -chloro- γ,β -allylic carbamates **135** by using β -chlorovinyl aldehydes **27** as a template. The carbamates **135** were prepared from their respective intermediates, the γ -chloro- γ,β -allylic alcohols **134**, which were isolable and *in situ* generated via reduction of **27** with NaBH₄ (Scheme 20).^[54] The structures of two of the allylic carbamates, were confirmed with the help of single-crystal X-ray diffraction.

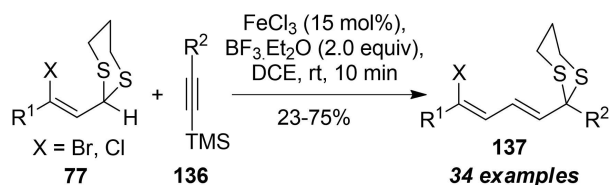
Tang group investigated a C₃ and C₁ coupling approach between vinyl 1,3-dithianes **77** and alkynylsilane derivatives **136** to generate the conjugated dienes **137** in good to excellent yields (Scheme 21).^[55] A diverse range of substituted (*E*)-1,3-dienes were obtained stereo-selectively using this method through regio-selective dual 1,3-sulfur migration process. It was



Scheme 19. Mechanism for the formation of α -functionalized enaminones.



Scheme 20. Synthesis of γ -chloro- γ,β -allylic carbamates *via* one-pot strategy.



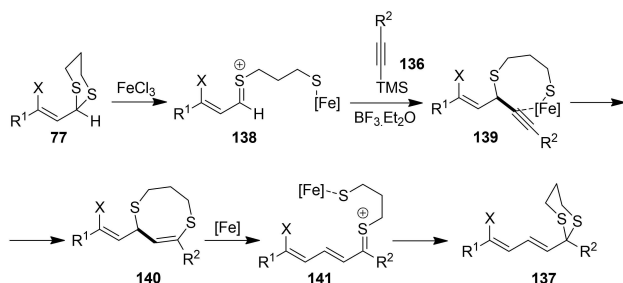
Scheme 21. Synthesis of highly substituted 1,3-dienes.

found that reaction proceeded through dual 1,3-sulfur rearrangement (Scheme 22).

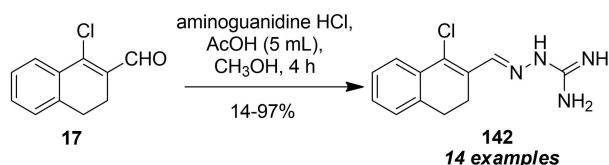
3.3.1. Synthesis of Imines Derivatives

Katzenellenbogen and co-workers observed that acidic conditions favoured the condensation reaction over substitution reaction (see Scheme 9). The reaction of β -chloro acroleins **17** with aminoguanidine.HCl yielded a series of guanylhazones **142** (Scheme 23).^[45] These guanylhazones were designed to block estrogen receptor (ER) activity and some of the hydrazones exhibited IC_{50} values in the low micromolar range.

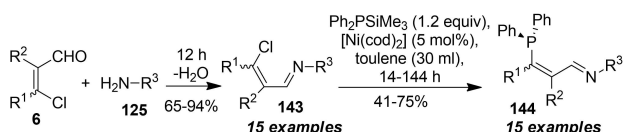
Schmidt and co-workers succeeded to synthesize α,β -unsaturated β -chloro-imines **143** via Schiff-base condensation. Conversion of imines into α,β -unsaturated 3-iminophosphine takes place by metal-catalyzed phosphorus-carbon cross-coupling through an addition–elimination sequence (Scheme 24).^[56] These resulting phosphine derivatives were identified as *E* or *Z*



Scheme 22. Dual 1,3-sulfur rearrangement for the synthesis of highly substituted 1,3-dienes.



Scheme 23. AcOH assisted synthesis of guanylhazones.

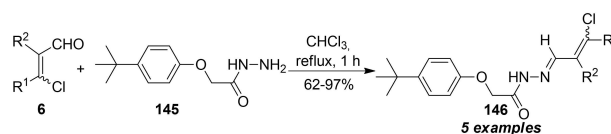


Scheme 24. Synthesis of α,β -unsaturated 3-iminophosphines.

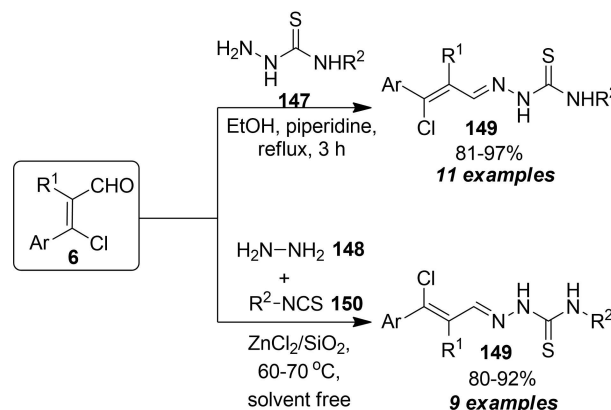
diastereomers alongside successfully isolating primarily single diastereomers for all the 15 new phosphine derivatives **144**. The X-ray single crystal analysis of α,β -unsaturated 3-iminophosphine proved their structures.

Hamzi group carried out the condensation of *tert*-butylphenoxyhydrazide **145** with β -chlorovinyl aldehydes/cinnamaldehydes **6** to furnish new acylhydrazones **146** (Scheme 25).^[57] NMR data revealed that *cis/trans*-amide conformers were formed because of N–C(O) bond rotation along with *E/Z* isomers about the C=C bond of β -chlorovinyl aldehydes. The effects of solvent polarity on the ratio of the *cis/trans*-amide rotamers was also inspected.

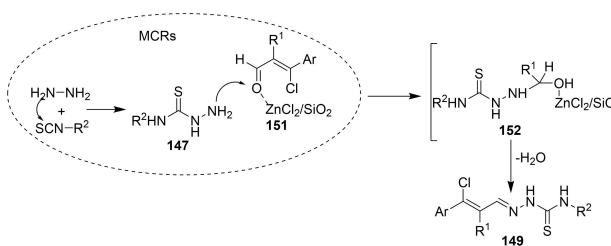
Sroor and co-workers synthesized a series of new thiosemicarbazone derivatives **149** as HCV 4WTG polymerase inhibitors. Thiosemicarbazones **149** were prepared using two different methods, first by reaction of different thiosemicarbazides **147** with β -chlorovinyl aldehydes **6** and the other by one-pot three component strategy under solvent free conditions using $ZnCl_2/SiO_2$ as a catalyst (Scheme 26).^[58] Mechanistic pathway for this reaction is shown in Scheme 27. It was realised that mild acidic and mild basic conditions were responsible for the preferred



Scheme 25. Synthesis of N-acylhazones.



Scheme 26. Synthesis of thiosemicarbazones.



Scheme 27. $ZnCl_2/SiO_2$ catalysed one-pot synthesis of thiosemicarbazone derivatives.

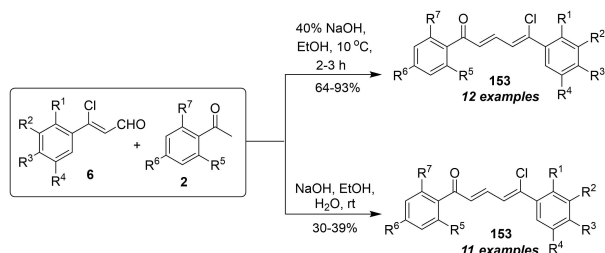
condensation reaction with formyl group instead of nucleophilic substitution reaction at β -halogen of β -chlorovinyl aldehydes **6**.

3.3.2. Synthesis of Chalcones

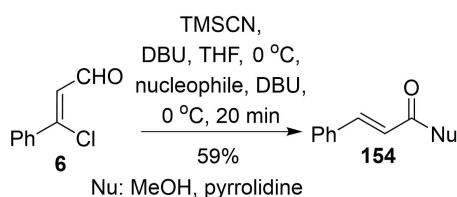
Bandgar group carried out the Claisen–Schmidt condensation of β -chlorovinyl aldehydes **6** with diversely substituted aryl ketones **2** which resulted in formation of densely conjugated chalcones **153** (Scheme 28).^[59] These compounds exhibited antimicrobial, anticancer as well as anti-inflammatory activities (against TNF- α and IL-6). CCK-8 cell lines were used to check out the cytotoxicity of synthesized compounds and they were found to be slightly toxic at 10 μ M concentration.

3.4. Functionalisation of β -halovinyl Aldehydes Through Reaction at Halogen as well as Formyl Group

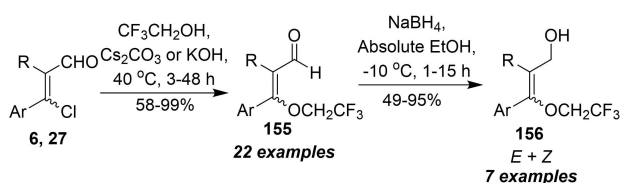
Fukuyama group recorded the redox transformation of β -chlorovinyl aldehydes **6** to corresponding carboxylic acid derivatives **154** via reaction with various nucleophiles in presence of TMSCN and DBU (Scheme 29).^[60] A selective switch to the stereochemistry of acyl group in the product was also noticed because of the temperature-dependent control of kinetic or thermodynamic protonation patterns.



Scheme 28. Synthesis of β -chlorovinyl chalcones.



Scheme 29. TMSCN and DBU assisted redox transformation of β -chloroacrolein.

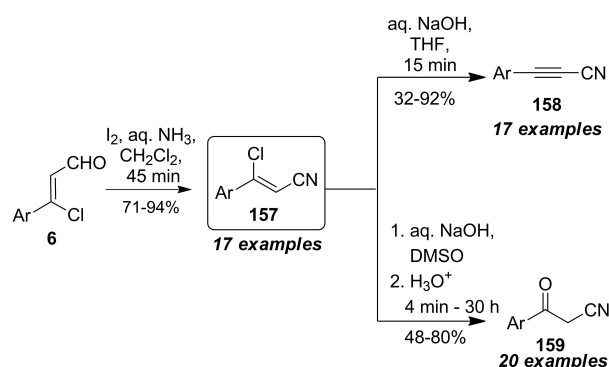


Scheme 30. Formation of β -fluoroalkoxy-acrylaldehyde and β -fluoroalkoxyallyl alcohols.

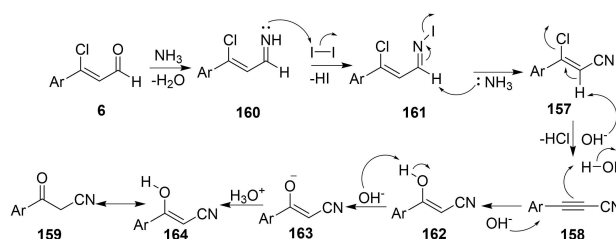
Slimi and co-workers demonstrated an appropriate method to synthesize a library of β -fluoroalkoxyvinyl aldehyde derivatives **155** and their corresponding alcohols **156** using β -chloroacrylaldehydes **6**, **27** through etherification and carbonyl group reduction reactions as depicted in Scheme 30.^[61] DFT methods were used to study mechanistic pathway of nucleophilic vinylic substitution reaction of the β -chlorovinyl aldehydes **6**. The presence of a hidden intermediate came into notice upon IRC analysis in accordance with a one kinetic step two-stage process. Small energy gap was found responsible for the isomerization of intermediate Z-3-chloro-3-phenylacrolein **156** into hidden intermediate E-3-chloro-3-phenylacrolein **156**.

Recently, our group developed a transition metal-free, highly efficient and straightforward one-pot strategy to synthesize propynenitriles **158** from β -chlorovinyl aldehydes **6**. It was revealed that the reaction proceeds through 3-chloropropenenitrile derivatives **157** which upon NaOH-promoted dehydrohalogenation furnished the propynenitriles **158** in 32–92% yields (Scheme 31).^[62a] In another study, we transformed the 3-chloropropenenitriles **157** into β -ketonitriles **159** using mild reaction conditions (Scheme 31).^[62b] This was found to be one of the most economic and environmental-friendly approach for synthesizing β -ketonitriles **159**. It was found that the reaction proceeded through iodine-assisted oxidative amination followed by base-promoted dehydrohalogenation and hydration of triple bond as depicted in Scheme 32.

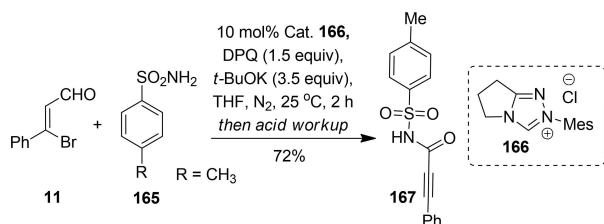
Ma group explored the unique reactivity of NHC catalyst **166** and developed a facile and effective route for the synthesis of three types of imides including N-sulfonylcarboxamides **167**, N-sulfinylcarboxamides, and dicarboximides in moderate to good yields via direct oxidative N-acylation of primary amides



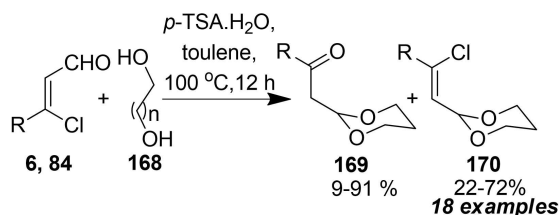
Scheme 31. Synthesis of propynenitriles and β -ketonitriles.



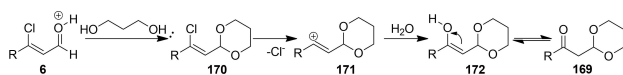
Scheme 32. Proposed reaction mechanism for the transformation of 3-chloropropenenitriles into propynenitriles and β -ketonitriles.



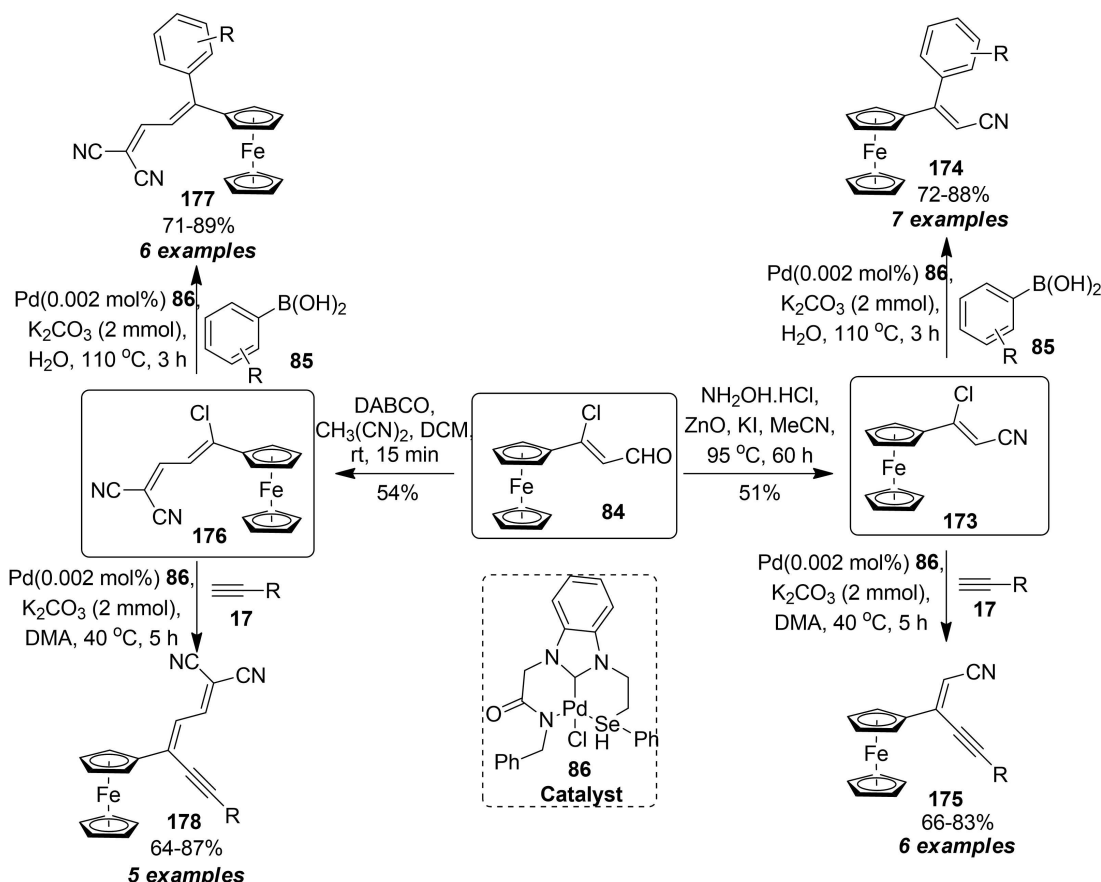
Scheme 33. Synthesis of N-sulfonylcarboxamides via direct oxidative N-acylation reaction.



Scheme 34. *p*-TSA catalyzed synthesis of β-ketoacetals.



Scheme 35. Mechanism for the formation of β-ketoacetals.



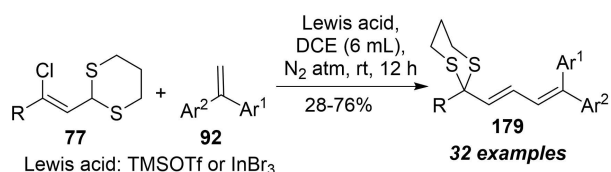
Scheme 36. Synthesis of 3-chloro-3-ferrocenylacrylonitrile and (3-chloro-3-ferrocenylallylidene)malononitrile.

with β-bromovinyl aldehydes **11** in presence of inorganic base and NHC catalyst **166** using DPQ as an oxidant (Scheme 33).^[63]

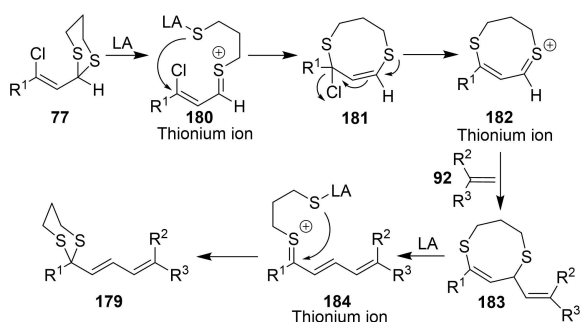
Srivastava group investigated the protection of formyl functionality in β-chlorovinyl aldehydes **6**, **84** with 1,2- and 1,3-diols **168** using *p*-TSA as a catalyst; however, β-ketoacetals **169** were obtained in moderate to excellent yields (Scheme 34).^[64] It was realised that reaction proceeded through the formation of β-chloroacetals **170** followed by dechlorination and addition of H₂O resulted in the formation of β-ketoacetals **169**. Remarkable transformation was achieved with electron releasing substituents attached at *para*-position of β-chlorovinyl aldehydes **6**, **84**. The selective generation of β-keto-1,3-acetal was also achieved with a mixture of 1,2- and 1,3- diols (Scheme 35). During this study, a very rare and unfamiliar multitasking property of *p*-TSA was observed.

Mathur group transformed (2-formyl-1-chlorovinyl)ferrocenes **84** into corresponding chloropropene nitrile derivatives **173** and investigated the Suzuki-Miyaura coupling with aryl-boronic acid **85** using selenated NHC-Pd(II) full pincer complex **86** as the catalytic system (Scheme 36).^[42] Some interesting results were obtained during Solvatochromic studies of the ferrocene derivatives.

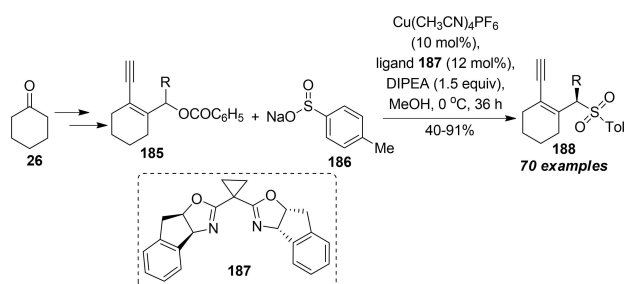
This group also synthesized ferrocenated enynes **91** using selenated NHC-Pd(II) full pincer complex **86** via Sonogashira cross-coupling reaction under copper-free and aerobic conditions (Scheme 36). They examined that 0.002 mol% of cata-



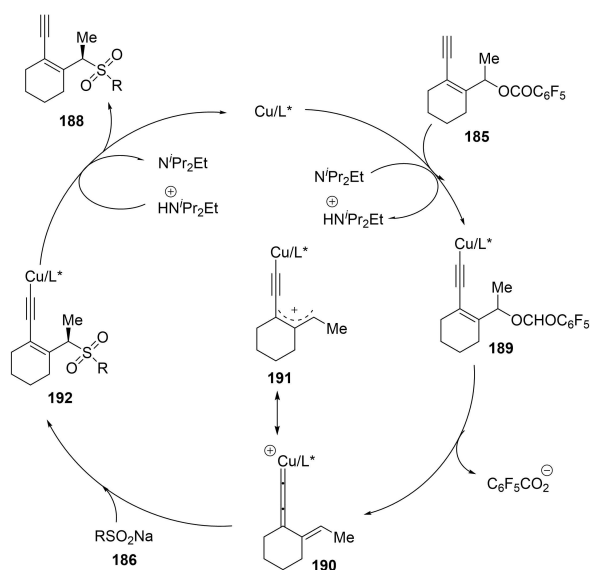
Scheme 37. Synthesis of 1,3-dithianyl substituted conjugated dienes.



Scheme 38. Proposed reaction mechanism for the formation of conjugated dienes.



Scheme 39. Cu-catalyzed synthesis of enantiomerically enriched chiral yne-allyl sulfone derivatives.



Scheme 40. Probable reaction mechanism.

lyst, selenated NHC–Pd(II) pincer complex **86** was more than enough for the coupling reaction under the areobic conditions within 5 hours and synthesized a library of 26 ferrocene substituted enynes **91** using this strategy. They also investigated the electrochemical responses of the generated products.^[43]

1,3-Dienes are popular substrates in many different biologically active compounds and interesting building block in synthetic chemistry. In this report, Tanga group, furnished 1,3-dithianyl substituted diene derivatives **179** via Lewis acids promoted dual 1,3-sulfur rearrangements (Scheme 37).^[65] Using this strategy, tri- and tetra-substituted 1,3-dienes were synthesized with excellent stereoselectivity (Scheme 38).

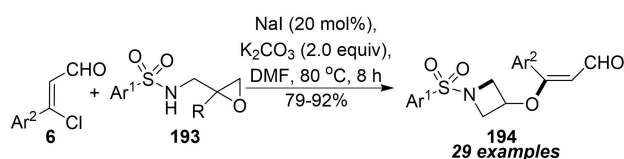
Asymmetric propargylic substitution reactions in asymmetric yne-allylic substitution has still remained as a challenging task. Lin group were the first who explored Cu-catalyzed remote enantioselective sulfonylation reaction of yne-allylic esters **185** with sodium sulfonates **186** (Scheme 39).^[66] This reaction proceeded through a copper-vinylvinylidene intermediate as presented in Scheme 40. This strategy exhibited stereo-, regio-, and enantio- selectivity along with easily accessible starting materials, easy to perform reaction conditions and vast substrate scope (70 examples).

4. Synthesis of Heterocycles

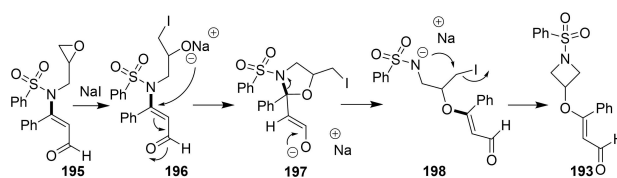
4.1. Synthesis of Three-membered Heterocycles

4.1.1. Synthesis of Azetidines

Swamy and co-workers carried out the transition metal-free reaction of N-oxiranylmethyl benzenesulfonamides **193** with β -chlorovinyl aldehydes **6** in presence of NaI/K₂CO₃ to produce the functionalized azetidines **194** (Scheme 41).^[67] It was proved that enamide (X-ray evidence) was formed as an intermediate during the ring expansion reaction between N-oxiranylmethyl benzenesulfonamide and β -chlorovinyl aldehydes (Scheme 42).



Scheme 41. Formation of functionalized azetidines.



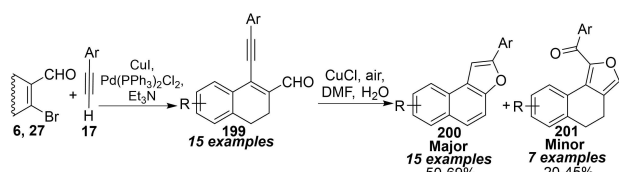
Scheme 42. Proposed reaction mechanism for the formation of functionalized azetidines.

4.2. Synthesis of Five-membered Heterocycles

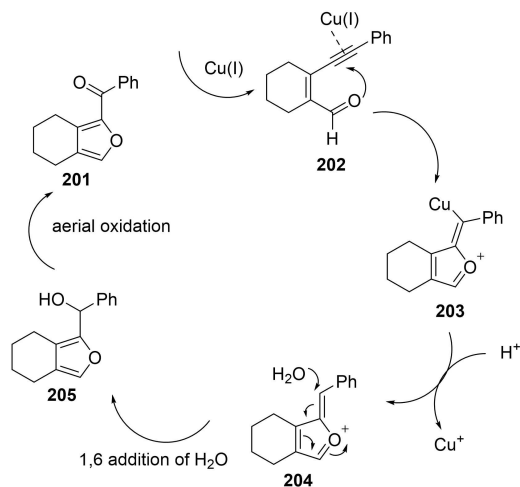
4.2.1. Synthesis of Furan Derivatives

Ray group developed a one-pot strategy to produce fused furans **201** via Cu-catalyzed reaction of *o*-alkynyl aldehydes **199** with water (Schemes 43–45).^[68] While a similar reaction involving addition of water as well as oxidation followed an unexpected cyclization process to yield the naphthofuran rings **200** (Scheme 45). Probable mechanism of the formation of furan and naphthofuran ring is shown in Schemes 44 and 45, respectively.

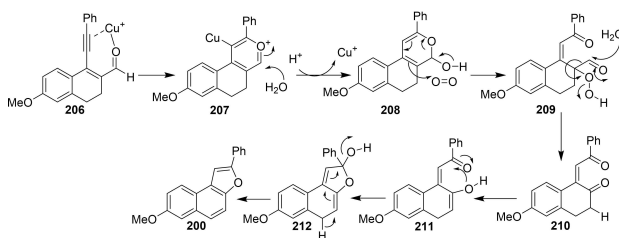
Slimi et al. performed the Vilsmeier-Haack reaction of alkyl pyruvates **22** in order to synthesize multifunctional ester containing β -chlorovinyl aldehydes **23**. This reaction was found to be highly stereoselective in nature and led to the formation of a 95:5 mixture of *Z* and *E* stereoisomers of β -chlorovinyl aldehydes. Interestingly, heating the 2-chloro-3-formylacrylate



Scheme 43. Cu-catalyzed synthesis of substituted furan and naphthofuran ring.



Scheme 44. Proposed mechanism for the formation of furan ring.



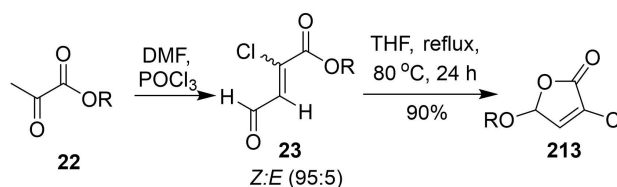
Scheme 45. Proposed mechanism for the formation of naphthofuran ring.

derivatives **23** in THF resulted into cyclic lactones, 3-chloro-5-alkoxy-2(5*H*)-dihydrofuran-2-one derivatives **213** (Scheme 46).^[69]

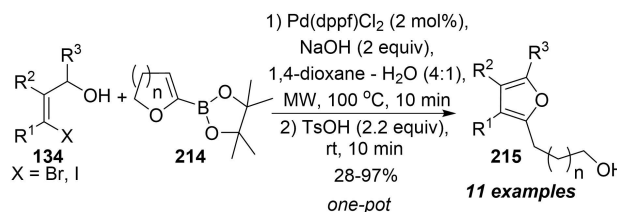
Cossy and co-workers carried out the tandem Suzuki-Miyaura coupling/acid-catalyzed cyclization to synthesize poly-substituted 2-(ω -hydroxyalkyl) furan derivatives **215** from substituted 3-haloallylic alcohols **134** and dihydropyran-, dihydrofuran-, or glycal-derived pinacol boronate derivatives **214** (Scheme 47).^[70] Mechanistic pathway is depicted in Scheme 48.

Swamy and his fellow researchers developed a facile K_3PO_4 -promoted route to generate trisubstituted furan derivatives **226** via addition of phosphites (H-phosphonate) **225** to *o*-alkynylaldehydes (enynals) **224** via a one-pot subsequential strategy through 5-*exo-dig* cyclization of the intermediates phosphonoalkynols **227** (Schemes 49 and 50).^[71]

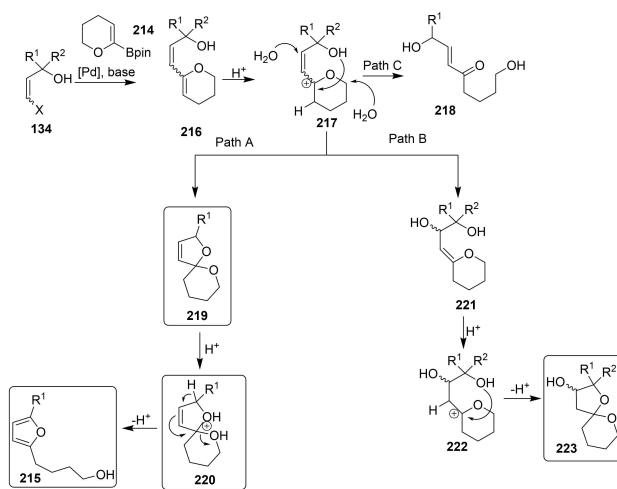
A facile approach to pyridine tethered furan derivatives **231** was delivered by Boruah group via one-pot reaction of β -bromo-acraldehydes **11** with 2-alkynylpyridines **230** in 55–65% yields. On modifying the reaction conditions to semi-aqueous,



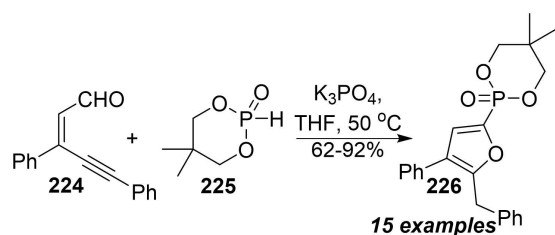
Scheme 46. Preparation of 3-chloro-5-alkoxy-2(5*H*)-dihydrofuran-2-one derivatives.



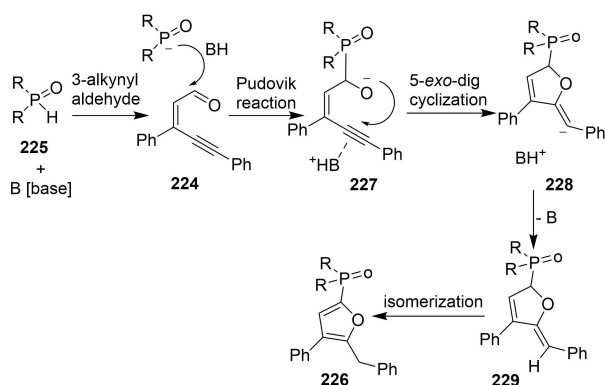
Scheme 47. Synthesis of furans via Suzuki-Miyaura coupling.



Scheme 48. Synthesis of furans via Suzuki-Miyaura.



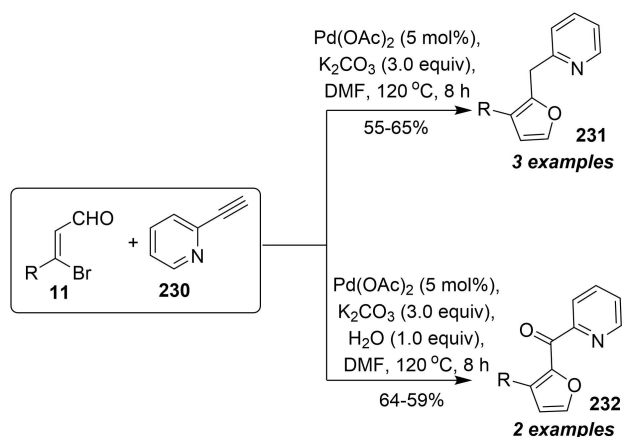
Scheme 49. Formation of trisubstituted phosphono-furan via 5-exo-dig cyclization.



Scheme 50. Proposed mechanism for the synthesis of phosphono-furans.

an effective route to 2-picolinoylpyrrole derivatives **232** was discovered (Scheme 51).^[72]

Swamy and co-workers also prepared 2,3-dihydrofurans **233** by carrying out a transition metal-free reaction between β -chlorovinyl aldehydes **6** with N-oxiranylmethyl benzenesulfonates



Scheme 51. Pd-catalysed synthesis of substituted furans.

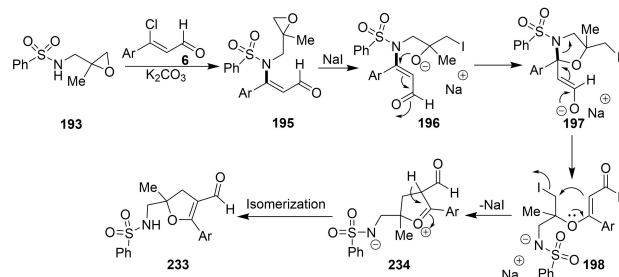


Scheme 52. Synthesis of 2,3-dihydrofurans.

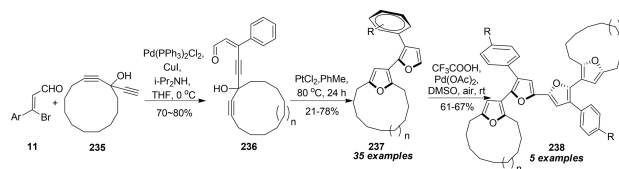
mides **193** using NaI/K₂CO₃ (Scheme 52) *via* a ring expansion reaction sequence as depicted in Scheme 53.^[67]

Heterophanes are important component in various natural compounds and drug molecules. Zhu and co-workers developed an interesting approach for the synthesis of [2,5]-furanophanes **237** having various ring types and ring sizes (Scheme 54). In this approach, furan-free precursors were used and reaction occurred *via* intramolecular carbene-mediated alkynyl migration and tandem cyclization process (Scheme 55).^[73] Additionally, through the oxidative coupling of products so obtained a series of tetrauran derivatives **238** can be produced.

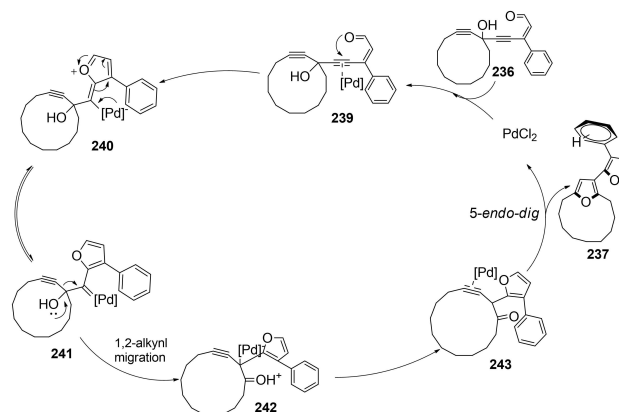
Zhu and co-workers prepared a library of well-defined poly-arylfunctionalized α -oligofuran derivatives **247–248**, where aryl groups were precisely introduced into each furan units *via* de novo synthesis of α -bi(arylfuran) monomers **246** (Scheme 56).^[74] Pre-installation of the necessary aryl groups in starting materials minimized the installation of laborious substituent in later stage. The synthesized α -oligo(arylfuran)s showed good capacity for hole transport and usage in organic light-emitting



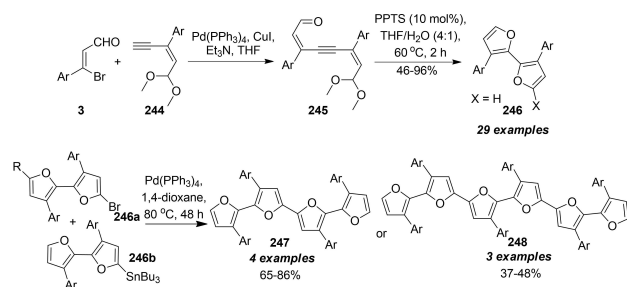
Scheme 53. Proposed mechanism for synthesizing 2,3-dihydrofurans.



Scheme 54. Synthesis of [2,5]-furanophane derivatives.



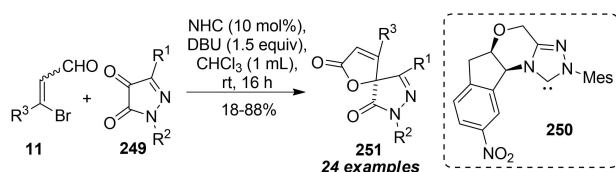
Scheme 55. Proposed reaction mechanism.



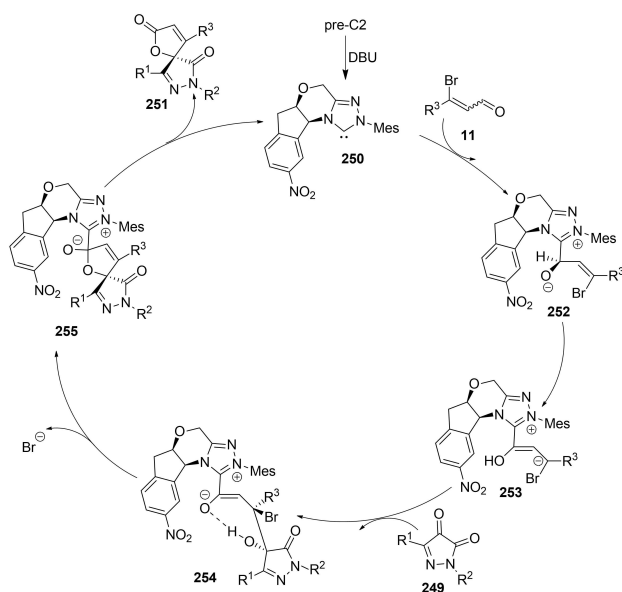
Scheme 56. Synthesis of tetrafurans and sexifurans.

diodes as hole-transporting layers, which indicated the significant application of α -oligofurans materials in OLEDs as *p*-type organic semiconductors.

Andrés and co-workers synthesized a series of chiral spiropyrrolone-butenolide derivatives **251** via NHC-catalyzed [3 + 2]-asymmetric annulation of β -bromovinyl aldehydes **11** with 1*H*-pyrazol-4,5-diones **249** (Scheme 57)^[75] in excellent yields (up to 88%) with high enantioselectivities (up to 97:3 er). The mechanism for the reaction has been showed in Scheme 58.



Scheme 57. NHC-catalyzed synthesis of spirocyclic pyrazolin-5-one derivatives.



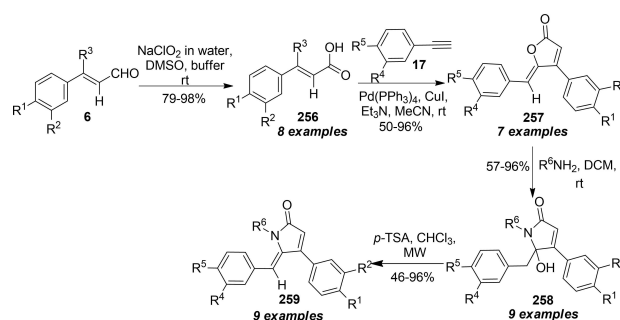
Scheme 58. Reaction mechanism for the formation of spirocyclic pyrazolin-5-ones.

4.2.2. Synthesis of Pyrrole Derivatives

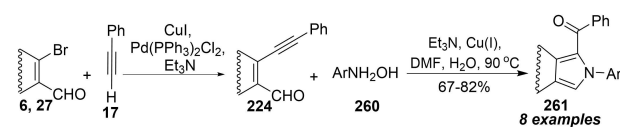
Gupton *et al.* demonstrated a method for synthesizing (*Z*)-5-benzylidene-4-arylpyrrol-2(*5H*)-one derivatives **259** starting from (*Z*)-3-aryl-3-haloenoic acids **256** which were in turn obtained from the corresponding (*Z*) β -chlorovinyl aldehydes **6**. The conversion of (*Z*)-3-aryl-3-haloenoic acids **256** into (*Z*)-5-benzylidene-4-aryl-5*H*-furan-2-one derivatives **257** was assisted by Pd-catalyst during Sonogashira coupling. The furanone derivatives so formed were eventually treated with primary amines and then undergo dehydration under microwave to furnish the (*Z*)-5-benzylidene-4-arylpyrrol-2(*5H*)-one derivatives **259** (Scheme 59).^[76]

Nandi and Ray reported a copper(I)-catalysed facile and effective approach for the synthesis of pyrroles **261** and isoindole derivatives. This strategy was found applicable to the synthesis of some quinone bearing annealed N-heterocyclic natural compounds (Scheme 60).^[77]

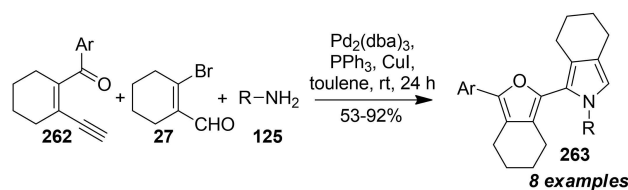
Ohe group explored a facile and advanced one-pot multi-component strategy for synthesizing hetero- α,α' -dimers of heterocycles **263** through Sonogashira coupling and double cyclization cascade including imine formation using Pd and Cu in catalytic amounts (Scheme 61).^[78] This reaction proceeded in a cascade manner under milder conditions, giving a synthetic tool for the assembly of π -conjugated system with a combination of palladium-catalyzed post-direct C–H bond arylations (Scheme 62).



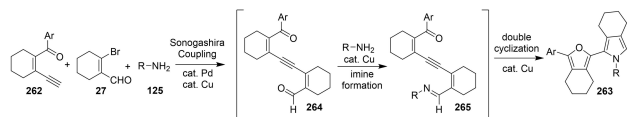
Scheme 59. Synthesis of (*Z*)-5-benzylidene pyrrol-2(*5H*)-one derivatives.



Scheme 60. Copper-catalyzed synthesis of substituted pyrroles.



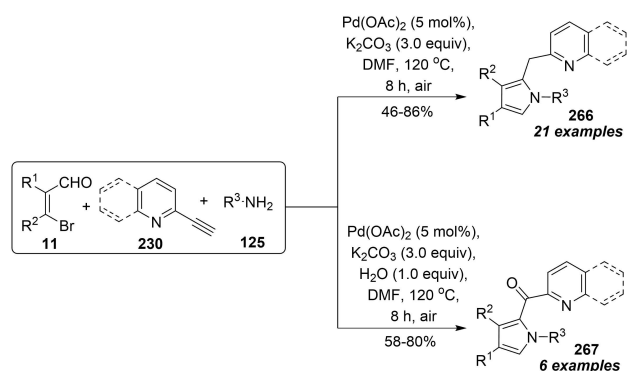
Scheme 61. Pd and Cu-catalyzed synthesis of 2-(2'-furyl)pyrroles via three-component coupling reactions.



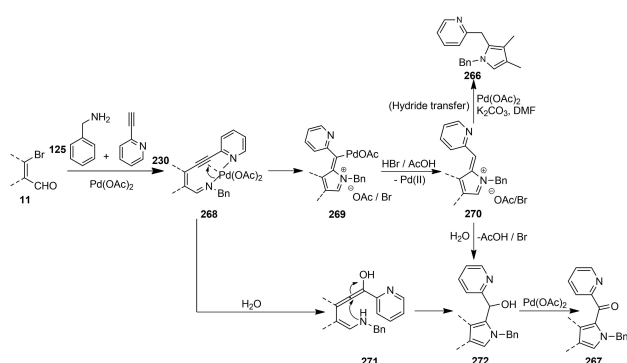
Scheme 62. Proposed reaction mechanism.

Boruha group also reported a facile methodology for the synthesis of alkylated pyridine-substituted pyrrole derivatives **266** via one-pot multi-component reaction of β -bromovinyl aldehydes **11** with primary amines **125** and 2-alkynylpyridines **230** in 46–85% yields. On modifying the reaction conditions to semiaqueous, it provided 2-picolinoylpyrrole derivatives **267** (Scheme 63).^[72] A probable mechanism for the synthesis of pyrrole derivatives **266–267** is shown in Scheme 64.

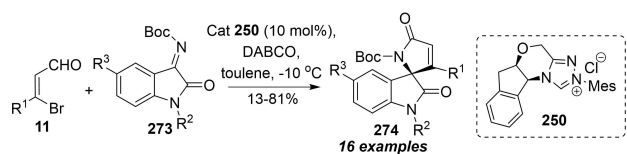
Hui group accomplished the synthesis of spiro[indoline-3,2'-pyrrole] derivatives **274** having quaternary chiral center via the asymmetric formal [3 + 2] annulation reaction of isatin N-Boc



Scheme 63. Synthesis of pyridine substituted pyrroles via one-pot multi-component strategy.



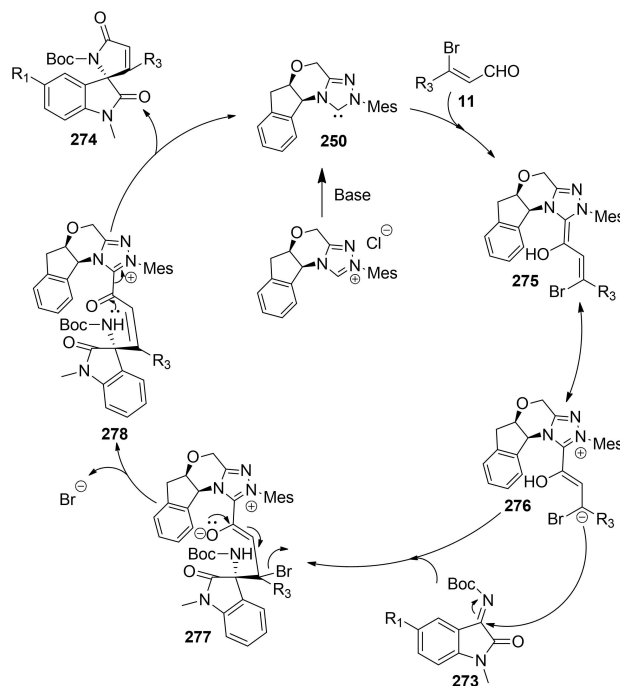
Scheme 64. Probable mechanism for synthesizing substituted pyrroles.



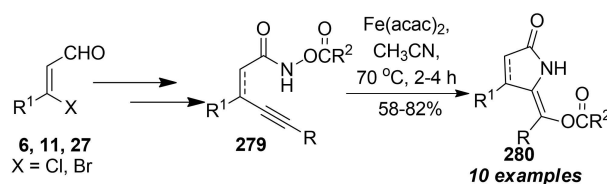
Scheme 65. NHC-catalyzed [3 + 2] annulations reaction of 3-bromoaldehydes with isatin ketimines.

ketimine derivatives **273** with β -bromovinyl aldehydes **11** under NHC catalysis **250** with excellent enantioselectivities (up to 99% ee) (Scheme 65).^[79] The possible mechanism the synthesis of spiro[indoline-3,2'-pyrrole] derivatives **274** is depicted in Scheme 66.

By using either thermally induced spontaneous or 4-(dimethylamino)pyridine-catalyzed O $\rightarrow$ O or O $\rightarrow$ N acyl group migration, Lee and co-workers succeeded to carry out intramolecular carboxyamidations of alkyne-tethered *O*-acylhydroxamates **279**. The carboxyamidation products **280** were readily obtained from both *Z*-alkene and arene-tethered substrates **279** in high yields under iron-catalyzed conditions (Scheme 67).^[80] The DFT calculations revealed that this iron-catalyzed carboxyamidation proceeded through a stepwise mechanism which involved iron-imidyl radical cyclization proceeded further by intramolecular acyloxy transfer from iron center to the alkenyl radical center to generate the *cis*-carboxyamidation products **280**.



Scheme 66. Probable catalytic cycle of the reaction.



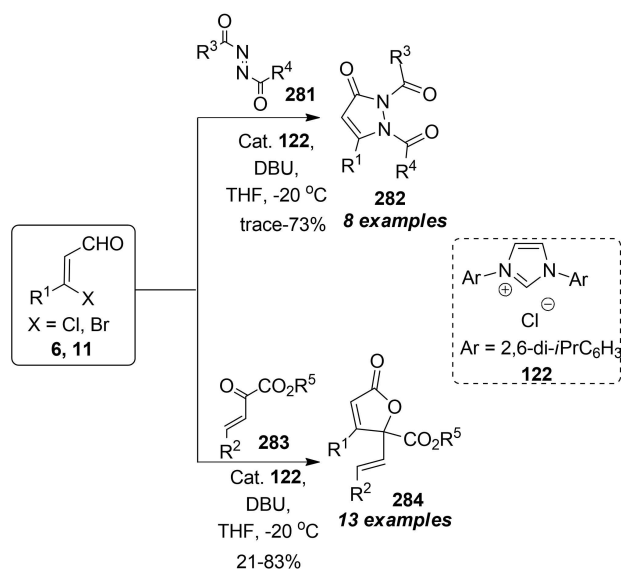
Scheme 67. Fe-catalyzed carboxyamidation.

4.2.3. Synthesis of Pyrazole Derivatives

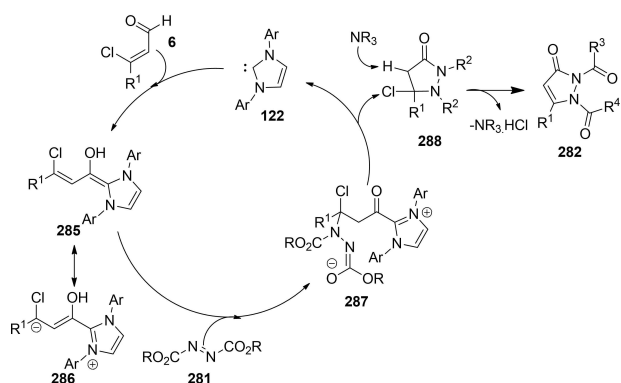
Ma and co-workers explored the synthetic utility of β -halovinyl aldehydes **6**, **11** for N-heterocyclic carbene **122** and DBU promoted reactions with azodicarboxylates **281** and β,γ -unsaturated α -keto esters **283** for the synthesis of pyrazolones **282** and butenolides **284** (Scheme 68).^[81] A probable mechanism for carrying out the mentioned reaction is presented in Scheme 69.

4.2.4. Synthesis of Thiophene/Selenophene Derivatives

Kirsch group transformed β -halovinyl aldehydes **6** into β -halovinyl nitriles **157** and reacted with sodium selenide in presence of suitable electrophile to generate the 2-nitroselenophen-3-amines **289** and 3-amino-2-selenophenecarbonitriles **290** and carried out further condensation/Friedlander annulation reaction with cycloalkanones **26** to provide Tacrine analogues **291** in a single operation. A comparative study



Scheme 68. NHC-catalyzed reactions of β -halovinyl aldehydes with β,γ -unsaturated α -keto esters and azodicarboxylates.

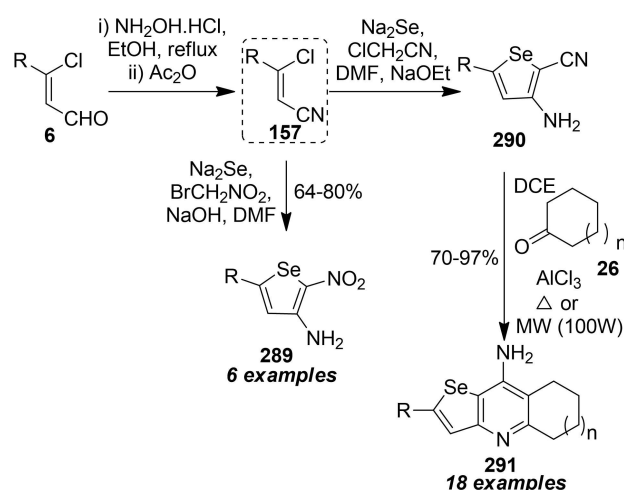


Scheme 69. Proposed reaction mechanism for the formation of pyrazolones.

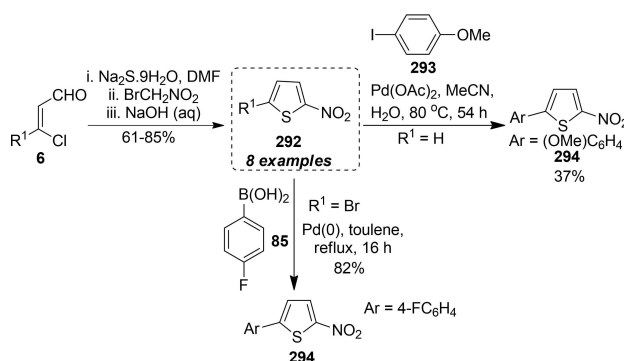
between classical heating and microwave irradiation was also put forward for the Friedländer condensation (Scheme 70).^[82]

In another study, this group demonstrated a one-pot methodology for the synthesis of new 2-aryl-5-nitrothiophene derivatives **294** starting from β -chlorovinyl aldehydes **6** (Scheme 71).^[83] β -chloro-vinyl aldehydes **6** were reacted with sodium sulfide and bromo nitromethane to furnish the nitrothiophene derivatives **292** which upon Heck and Suzuki coupling furnished the 2-aryl-5-nitrothiophene derivatives **294**.

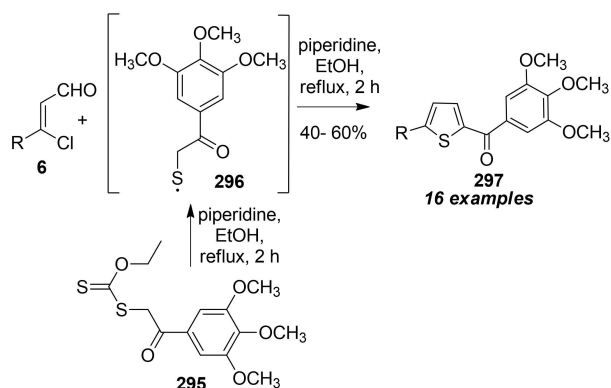
Romagnoli group succeeded to synthesize a series of biaryl ketones **297** that were analogous to chalcones using β -chlorovinyl aldehydes **6** and O-ethyl S-(2-oxo-2-(3,4,5-trimethoxyphenyl)ethyl) carbonodithioate **295** as the precursor, in which enone system's double bond was embedded within a thiophene ring, and they analysed their antiproliferative activity and hampering of tubulin assembly and colchicine binding to tubulin (Scheme 72).^[84] Interestingly, the synthesized biaryl ketones **397** inhibited the growth of various cancer cell lines at nanomolar to low micromolar concentrations. Generally, all molecules exhibited significant antiproliferative activity and inhibited tubulin polymerization with an IC₅₀ < 2 μ M. Some of these molecules caused K562 cells to seize in the G2/M phase of the cell cycle.



Scheme 70. Synthesis of tacrine analogues.

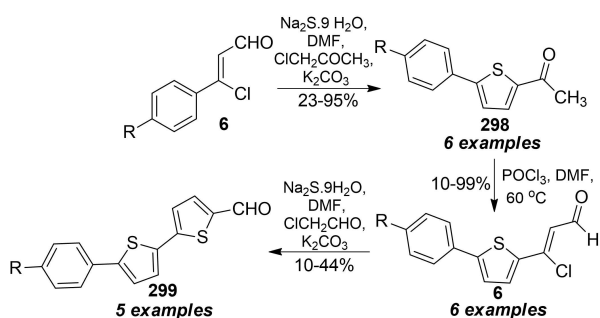


Scheme 71. Synthesis of 2-aryl-5-nitrothiophenes.

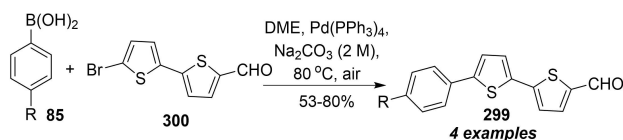


Scheme 72. Synthesis of thiophene derivatives as anticancer agents.

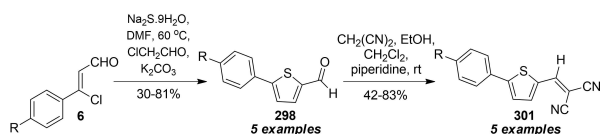
A library of formyl-substituted 5-aryl-2,2'-bithiophene derivatives **307** was reported by Raposo and co-workers through two different approaches *via* Vilsmeier–Haack–Arnold reaction (VHA) or using Suzuki cross-coupling reaction. It was noted that synthesized compounds **307** were obtained in low yields *via* Vilsmeier–Haack–Arnold reaction, through starting with readily accessible β -chloro-vinyl aldehydes **6** as the precursor (Scheme 73).^[85] Whereas formyl-arylthiophenes **307** were obtained in good yields *via* Suzuki coupling between functionalized arylboronic acids **85** and 5-bromo-5'-formyl-2,2'-bithiophene **300** in a single step (Scheme 74).^[85]



Scheme 73. Synthesis of formyl-arylthiophenes *via* Vilsmeier–Haack–Arnold reactions.



Scheme 74. Synthesis of formyl-arylthiophenes *via* Suzuki coupling.



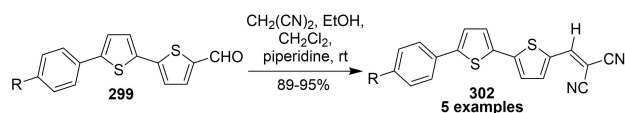
Scheme 75. Preparation of dicyanovinyl-arylthiophene *via* Knoevenagel condensation.

In an extension to this study, Raposo group prepared a library of two dicyanovinyl-substituted molecules; 2-aryl-5-dicyanovinylthiophene derivatives **301** and 5-aryl-5'-dicyanovinyl-2,2'-bithiophene derivatives **302** *via* Knoevenagel condensation of 2-aryl-5-formylthiophene derivatives **298** and 5-aryl-5'-formyl-2,2'-bithiophenes **299** with malononitrile as presented in Schemes 75 and 76.^[86]

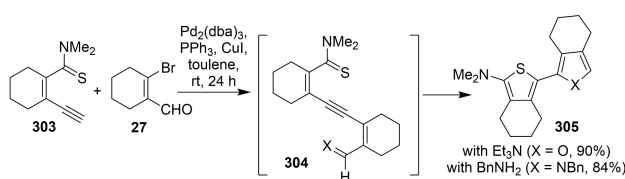
Ohe group developed a facile strategy for the synthesis of hetero- α,α' -dimers of heterocycles (2-(5'-thienyl)furan and 2-(5'-thienyl)pyrroles) **305** through Sonogashira coupling and double cyclization cascade including imine formation using Pd and Cu catalysts. This reaction cascade proceeded under milder conditions, providing a synthetic tool for the assembly of π -conjugated system with a combination of palladium-catalyzed post-direct CH bond arylations (Scheme 77).^[78]

Gogoi and co-workers demonstrated a metal-free cascade methodology for synthesizing unorthodox polycyclic 2-formylthiophene derivatives **307** starting from β -halovinyl aldehydes **6**, **27** and 1,4-dithiane-2,5-diols **306**. A recyclable polymer supported organic base was employed to prepare polycyclic 2-formylthiophene derivatives **307** (Scheme 78).^[87] This strategy was found applicable to synthesis of various advanced polycyclic thiophene derivatives consisting of steroidal D-ring annelated thiophenes **307** in high yields. It was found that reaction proceeded through addition-elimination reaction followed by Knoevenagel condensation (Scheme 79).

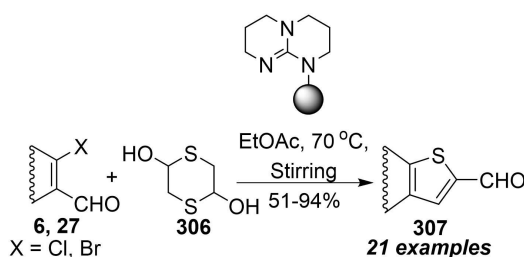
Gong and co-workers developed an important synthetic route for the production of 2-nitrothiophene derivatives **292** *via* a tetra-*n*-butylammonium fluoride-promoted or DIEA-assisted



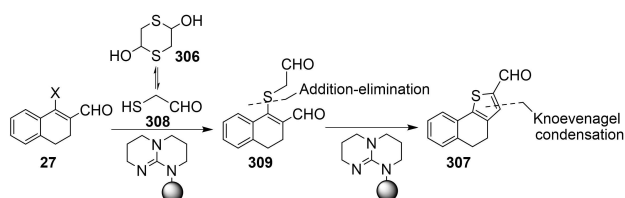
Scheme 76. Synthesis of dicyanovinyl-arylthiophene derivatives.



Scheme 77. Synthesis of 2-(5'-thienyl)furan and 2-(5'-thienyl)pyrrole *via* tandem coupling reactions.



Scheme 78. Synthesis of polycyclic 2-formylthiophenes using a polymer-supported organic base.

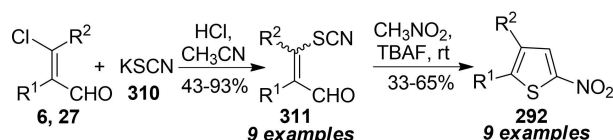


Scheme 79. Proposed reaction mechanism for synthesizing 2-formylthiophenes.

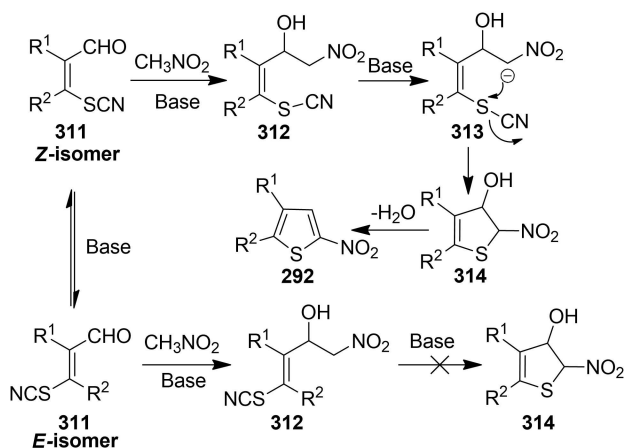
tandem Henry reaction and nucleophilic substitution reaction of nitromethane with 3-thiocyanatoacroleins **311**, which were synthesized by the displacement reaction of β -chlorovinyl aldehydes **6**, **27** with potassium thiocyanate **310** under mild acidic conditions (Scheme 80).^[88] A proposed mechanism is depicted in Scheme 81.

4.2.5. Synthesis of Oxazole and Isoxazole Derivatives

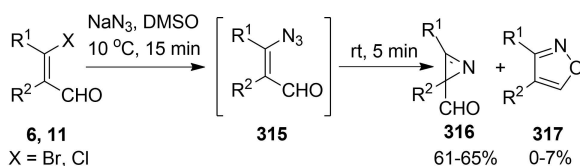
Brahama and Ray developed a facile and easy to perform methodology for the synthesis of azirine aldehydes **316**, **318**



Scheme 80. Synthesis of 2-nitrothiophenes from β -chlorovinyl aldehydes.



Scheme 81. Mechanism for the synthesis of 2-nitrothiophenes from β -chlorovinyl aldehydes.



Scheme 82. Synthesis of azirine aldehydes.

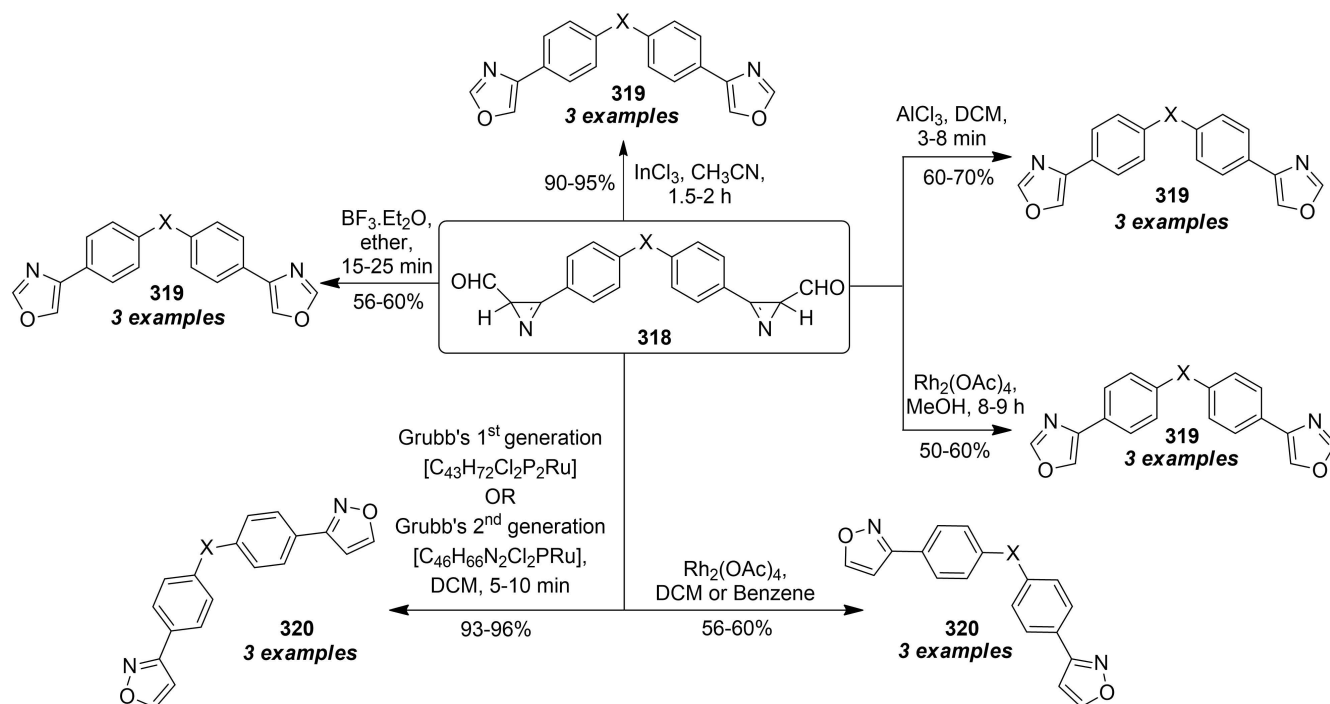
starting from β -bromo/chlorovinyl carbaldehydes **6**, **11** at ambient temperature. It was found that different transition metal catalysts and a diverse range of Lewis acids can be used to transform 2-formyl-azirine derivatives **316**, **318** into oxazole and isoxazole derivatives (Schemes 82 and 83).^[89] Mechanism for this protocol has been outlined in Scheme 84 where it has been proposed that in presence of $\text{Rh}(\text{OAc})_4$ initial π -complexation of $\text{Rh}(\text{II})$ catalyst with the imino nitrogen takes place which is then followed by the ring opening giving intermediate **322** which further results in N–O bond formation with the regeneration of rhodium complex to yield the isoxazole framework **317**. On the other hand, the mechanism in presence of Lewis acid was not clear and it was proposed that coordination of azirine aldehydic oxygen with Lewis acid results in initiation of ring transformation reaction to yield a bicyclic intermediate **324** which dissociate to **325** which on further addition of water followed by dehydration yielded the oxazole framework **328**.

Fray et al. carried out the reaction of β -chlorovinyl aldehydes **6** with hydrazides **145** intended to prepare novel α,β -unsaturated-2,5-disubstituted-1,3,4-oxadiazoles **329** and it was found that the desired 1,3,4-oxadiazoles **329** can be prepared via I_2 -promoted cyclisation of *cis/trans*-amide hydrazones (Scheme 85).^[90] The *in vivo* antitumor activity of some compounds was evaluated and were found to be non-toxic for liver as well as kidney; however, hepato/nephrotoxicity was noticed in mice treated with a dose of 100 mg/kg.

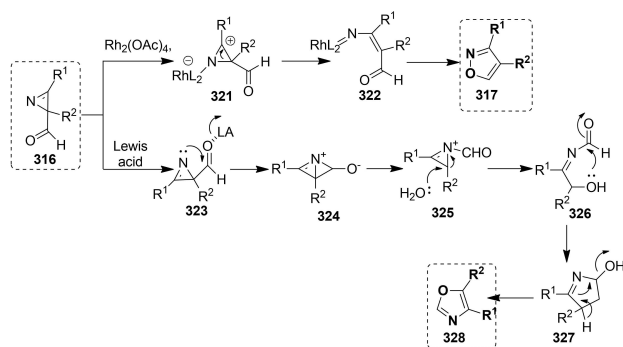
Wazalwar group also synthesized a series of isoxazole derivatives **330** and carried out their molecular docking studies using erlotinib, gemcitabine and ketoconazole as the reference drugs (Scheme 86).^[91] The molecular docking studies of all nine compounds showed good docking score as compared to standard drugs. It was then found that 4-OH and 4-F derivatives showed great affinity for all six CYP450 proteins under study. 4-F and 3- NO_2 derivatives were found to be most appropriate lead compound for the inhibition of CYP1 A2 followed by 4-OH derivatives. 4-OH derivatives having significant binding capability showed encouraging inhibition of CYP1 A2, CYP2 C9, CYP2 C8, CYP2 C19 and CYP2D6. On carrying out a detailed crystal structure study it was revealed that five of the synthesized isoxazole derivatives gave a clear understanding about the solid-state structural features.

4.2.6. Synthesis of Thiazole Derivatives

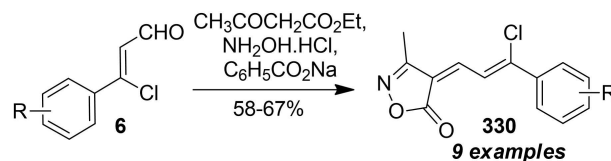
To combat the uncontrolled infections of *Mycobacterium tuberculosis* (Mtb) and inflammations caused by the production of radical species during Mtb infection, Hublikar *et al.* developed a library of (*E*)-2-(2-allylidenehydrazinyl)thiazoles **332** via one-pot multicomponent assembly of β -chlorovinyl aldehydes **6** with phenacyl bromides **331** and hydrazinecarbothioamide **147** (Scheme 87).^[92] The library of compounds was prepared with a significant variation in LogP values, and then analyzed their drug-likeness. The *in vitro* inhibition potentials were evaluated against Mtb H37Rv by the microplate Alamar Blue assay. The radical scavenging properties were also studied in order to establish the dual-action properties of the molecules.



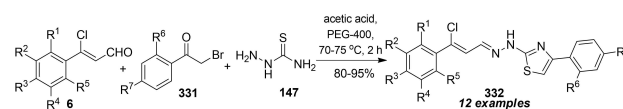
Scheme 83. Rearrangement of azirine aldehydes into oxazole and isoxazole derivatives.



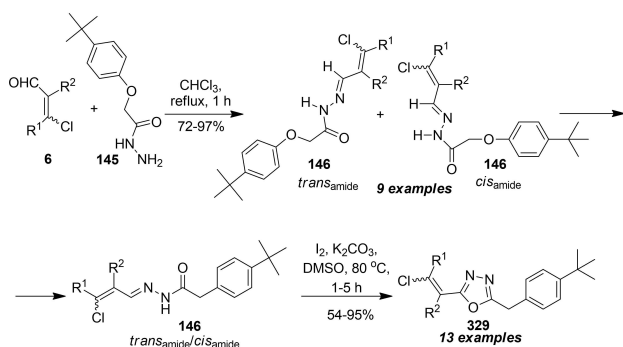
Scheme 84. Proposed mechanism for the rearrangement of azirine aldehydes into oxazole and isoxazole derivatives.



Scheme 86. Synthesis of isoxazole derivatives.



Scheme 87. One-pot synthesis of thiazoles.



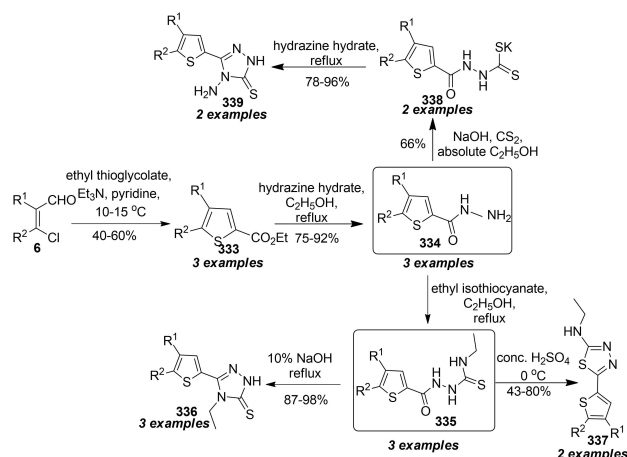
Scheme 85. Formation of α,β -unsaturated 2,5-disubstituted 1,3-oxadiazole derivatives.

Mavrova *et al.* developed a method for the synthesis of various 4,5-substituted-1,2,4-triazole-thione derivatives **336**, **339**

and 2,5-substituted-1,3,4-thiadiazole derivatives **337** and analyzed their cytotoxic properties (Scheme 88).^[93] It was noted that some of the compounds including 4-ethyl-5-(4,5,6,7-tetrahydro-1-benzothien-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thiones exhibited high cytotoxicity under *in vitro* conditions against thymocytes with IC_{50} values of 0.46 μ M, 5.2×10^{-6} μ M, 0.012 μ M and 1.0×10^{-6} μ M.

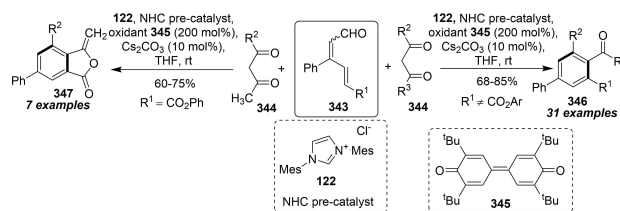
4.2.7. Synthesis of Triazole Derivatives

In order to improve potency and their selectivity as carbonic anhydrase inhibitors, Sharma group explored the synthetic potential of β -chlorovinyl aldehydes **6** and prepared a library of 20 novel 1,2,3-triazole benzenesulfonamide derivatives **340**–**342** having different functionalities like nitrile, carbothioamide, and *N'*-hydroxycarboximidamide as depicted in Scheme 89.^[94] In



Scheme 88. Synthesis of 1,3,4-thiadiazoles.

vitro testing of synthesized 1,2,3-triazole derivatives was carried out as CAls in resistance to four physiologically and pharmacologically linked isoforms of human carbonic anhydrase (hCA I, II, IV, and IX). Some compounds exhibited variable inhibition constants varying from 8.1 nM to 3.22 μ M for hCA I, 4.7 nM to 0.50 μ M for hCA II, 15.0 nM to 3.7 μ M for hCA IV, and 29.6 nM to 0.27 μ M for hCA IX.



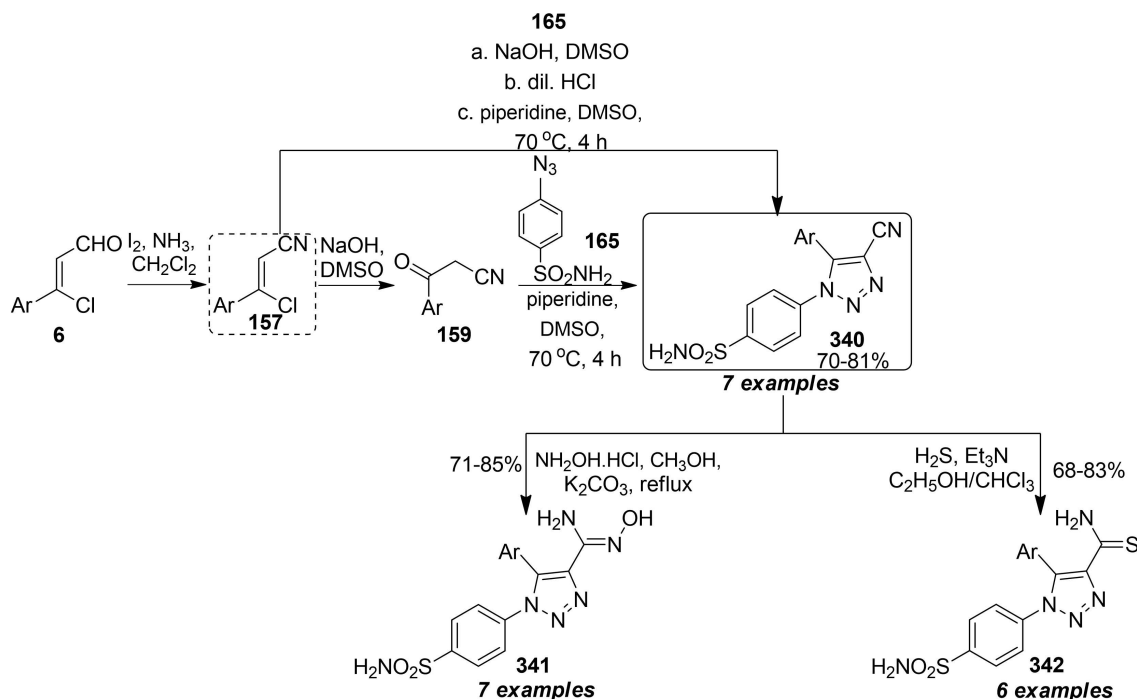
Scheme 90. NHC-catalyzed formation of multi-substituted benzene derivatives via δ -carbon activation.

4.3. Synthesis of Six-membered

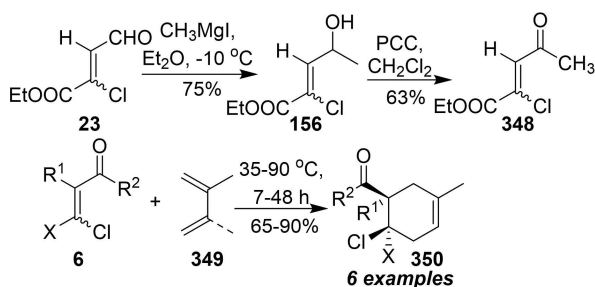
4.3.1. Synthesis of Benzene Derivatives

Chi group carried out a NHC 122 catalyzed domino reaction via a δ -LUMO activation of $\alpha,\beta,\gamma,\delta$ -diunsaturated enal 343 for the formal [4 + 2] formation of differently-substituted arene derivatives 346 and 3-ylidenephthalides 347 (Scheme 90).^[95] The reaction proceeded in a very regio- and chemo- selective manner through two different catalytic pathways depending upon the nature of substrate 344.

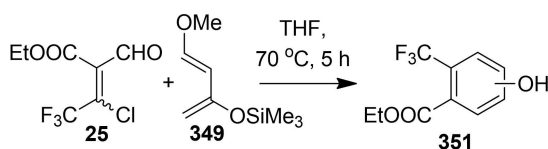
Slimi and co-workers investigated the Diels-Alder reaction of β -chlorovinyl aldehydes 23 and 25 with conjugated dienes 349 to afford the highly functionalized cyclohexene derivatives 350 (Scheme 91),^[96] exhibiting quaternary centers, with good to excellent yields. Furthermore dehydrochlorination of these cycloadducts (CAs) 352 and subsequent DBU-assisted aromatization yielded the substituted benzene derivatives 351 (Scheme 92).^[96] By using 1D, 2D and hetero nOe NMR techniques, confirmation of structures of isomers were carried out based on the NMR chemical shifts and coupling constant



Scheme 89. Synthesis of 1,2,3-triazole benzenesulfonamides as carbonic anhydrase inhibitors.

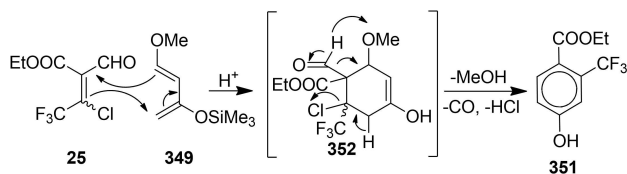


Scheme 91. Diels-Alder synthesis of cyclohexene derivatives.

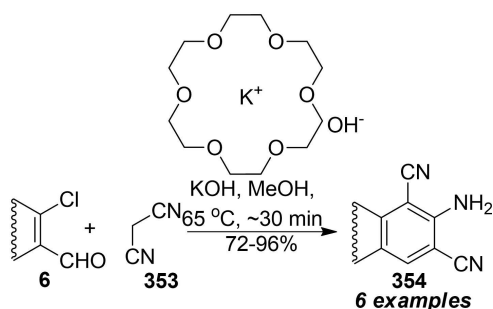


Scheme 92. Reaction of Danishefsky's diene with β-chlorovinyl aldehydes to generate benzene derivatives.

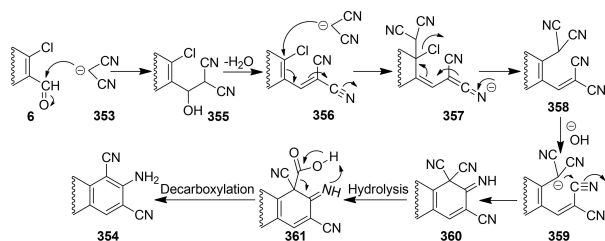
values. A possible mechanism for the synthesis of benzene derivatives is depicted in Scheme 93.



Scheme 93. Probable reaction mechanism.



Scheme 94. Synthesis of dicyanoaniline derivatives from β-chloro-α,β-unsaturated aldehydes.



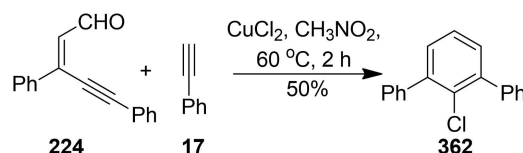
Scheme 95. Proposed mechanism for the formation of dicyanoaniline derivatives.

Kundu *et al.* described a two-component domino strategy for the synthesis of 2,6-dicyanoaniline derivatives **354** via reaction of malononitrile **353** with β-chlorovinyl aldehydes **6** by using KOH-18-crown-6 in catalytic amount in methanol (Scheme 94).^[97] On carrying out the *in-vitro* intercalation studies of 3-amino-9,10-dihydrophenanthrene-2,4-dicarbonitrile derivatives **354** with Calf-Thymus DNA, it came into notice that this moiety interacted with greater affinity than ethidium bromide (EtBr). The mechanism for the synthesis of 2,6-dicyanoaniline derivatives **354** is shown in Scheme 95.

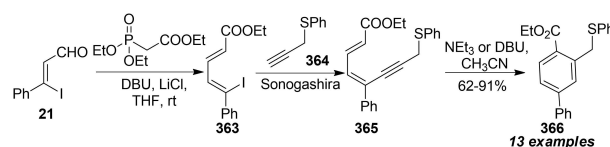
Asao group carried out the CuCl₂-assisted reaction of enynals **224**, (*ortho*-alkynylaldehydes) with terminal alkynes **17** in order to generate a variety of haloaromatic molecules **362** stereoselectivity with moderate to excellent yields. 2,2'-Binaphthyl skeletons were also prepared easily by the reaction of *ortho*-alkynylbenzaldehyde derivatives and diynes (Scheme 96).^[98] The same method was employed to synthesize poly-substituted tetracenes.

Zhou group revealed a simple and effective procedure for obtaining polyfunctionalized benzenes and naphthalenes **366** via electrocyclization reaction (Scheme 97).^[99] This kind of reaction has great applicability in organic synthesis because of the easily accessible starting materials and simple functioning.

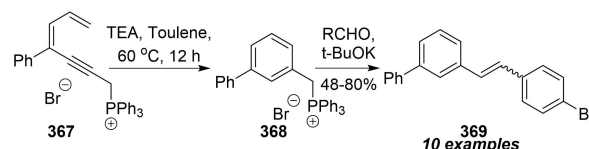
Highly functionalized phosphonium salts are not easily accessible even though they have wide range of utility in organic synthesis. Keeping an eye on this, Zhoua group demonstrated a one-pot methodology for synthesizing poly-substituted vinylbenzene derivatives **369** via a sequence of propargyl-allenyl isomerizations and electrocyclizations of phosphonium salts **367**. Further Wittig reactions with aromatic aldehydes led to the formation of stilbene derivatives **369** (Scheme 98).^[100] Mechanism for this reaction is depicted in Scheme 99.



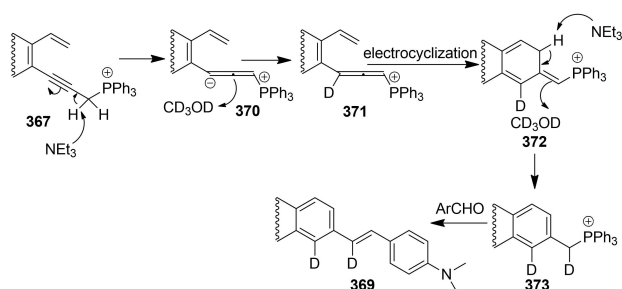
Scheme 96. CuCl₂ mediated production of benzene frameworks.



Scheme 97. Synthesis of polyfunctionalized benzenes.

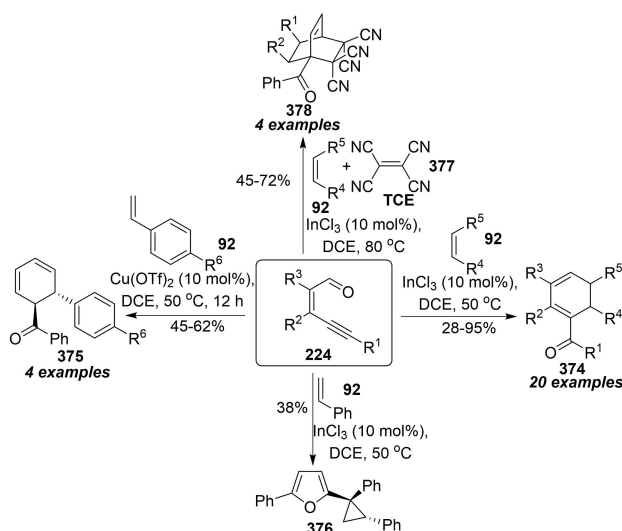


Scheme 98. Synthesis of polysubstituted vinylbenzenes.

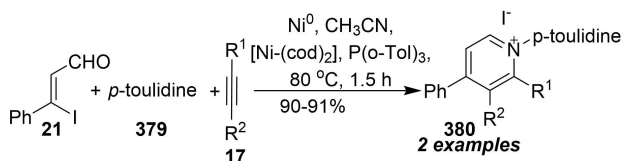


Scheme 99. Probable mechanism for the formation of vinylbenzenes.

Zhu and colleagues developed an excellent methodology that was metal-dependent and achieved the synthesis of multisubstituted cyclohexadiene derivatives **374–375**. 1,3-Cyclohexadiene (1,3-CHD) derivatives **374–375** were obtained via gold/indium catalysed reaction while 4-cyclohexadiene (2,4-CHD) derivatives **375** were generated upon using $\text{Cu}(\text{OTf})_2$ as a catalyst. When electron-deficient tetra-cyanoethylene was added, cyclohexadiene was trapped and this one-pot, three-component reaction affording the bridged product **378**. The furan linked cyclopropanation products **376** could be obtained during reaction in presence of InCl_3 showing the formation of a carbene intermediate (Scheme 100).^[101]



Scheme 100. Metal-catalyzed synthesis of 1,3-cyclohexadiene derivatives.



Scheme 101. Multicomponent synthesis of pyridinium salts.

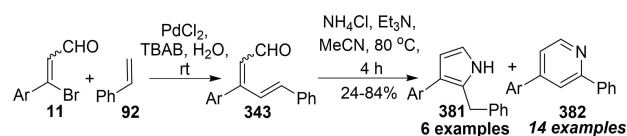
4.3.2. Synthesis of Pyridine and Isoquinoline Derivatives

Cheng and co-workers explored the β -iodovinyl aldehydes and developed a regioselective nickel-catalyzed reaction of *o*-halobenzaldimine derivatives with diverse alkynes **17** for the synthesis of pyridinium/isoquinolinium salts **380** with high atom economy (Scheme 101).^[102] These salts were then easily reduced to their corresponding reductive homo-coupling compounds and oxidized to pyridine/isoquinolinone derivatives.

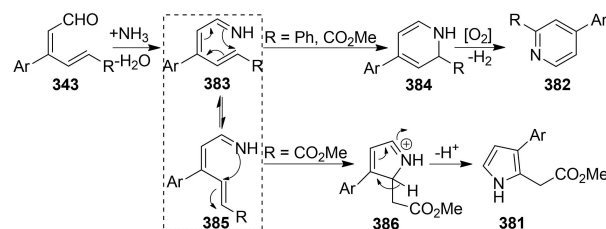
Singha group succeeded in carrying out the synthesis of 2,4-disubstituted pyridines **382** as well as pyrrole derivatives **381** by initiating the reaction between different β -bromovinyl aldehydes **343**, alkenes and ammonium chloride in the presence of Et_3N in ACN under air at 80 °C (Scheme 102).^[103] Probable mechanism for this reaction has been depicted in Scheme 103.

Shekarrao group carried out the multi-component reaction of steroidal/nonsteroidal β -halovinyl aldehyde **387**, alkynes **17** and benzylamine **125** to generate the steroidal D-ring fused 5,6-disubstituted pyridine derivatives and nonsteroidal substituted pyridine derivatives **388** under solvent free conditions using $\text{Pd}(\text{OAc})_2$ as the catalyst under MW irradiation (Scheme 104).^[104] Mechanism for carrying out this reaction is shown in Scheme 105.

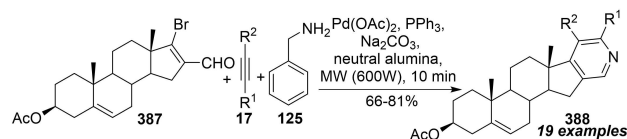
Dhara and co-workers demonstrated a one-pot methodology to achieve isoquinoline derivatives **403** through Cu-mediated tandem cross-coupling and cyclization under milder reaction conditions. A multicomponent annulation of β -bromovinyl aldehydes **11**, **27**, aq NH_3 and terminal alkynes **17** in presence of $\text{CuI}/1,10$ -phenanthroline as the catalytic system



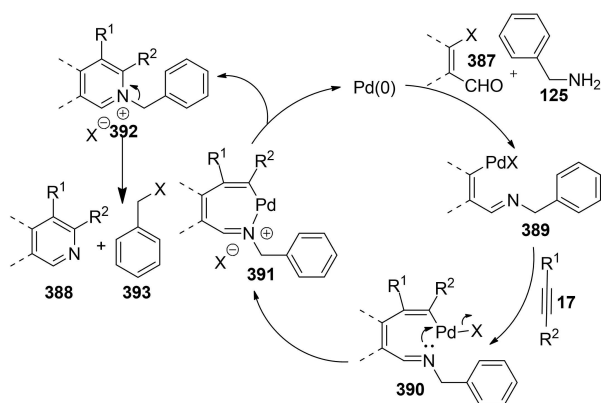
Scheme 102. Synthesis of pyridine and pyrrole derivatives.



Scheme 103. Proposed mechanism for the formation of pyridine and pyrrole derivatives.

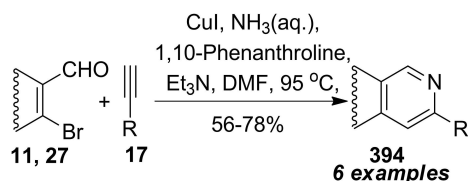


Scheme 104. Pd-catalyzed formation of steroidal fused pyridine derivatives.

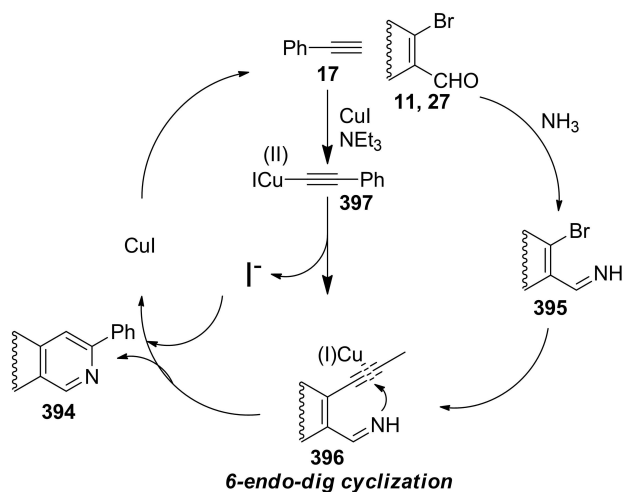


Scheme 105. Probable mechanism for the synthesis of steroidal D-ring fused pyridine derivatives *via* Pd catalysis.

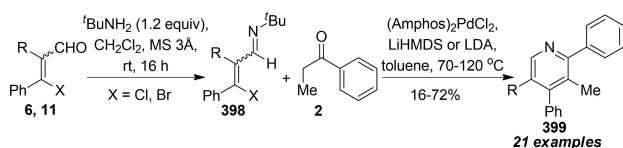
furnished the substituted isoquinolines **403** with great regioselectivity in 56–78% yields (Scheme 106).^[105] A probable mechanism for the reaction is depicted in Scheme 107.



Scheme 106. Cu-catalyzed 3-component synthesis of isoquinoline derivatives.



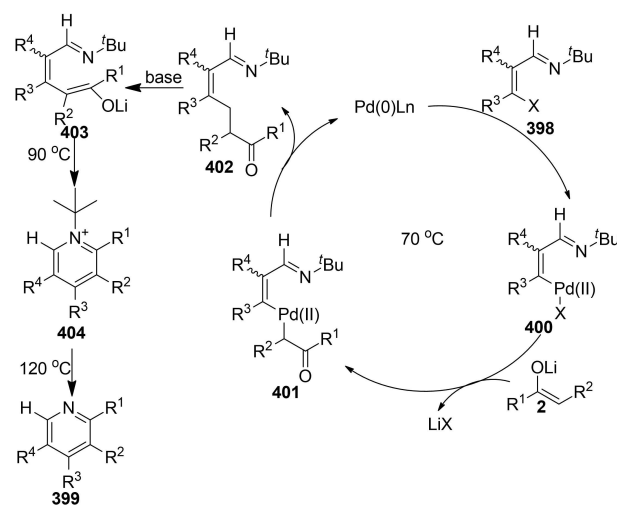
Scheme 107. Probable reaction mechanism for Cu-catalyzed isoquinoline formation.



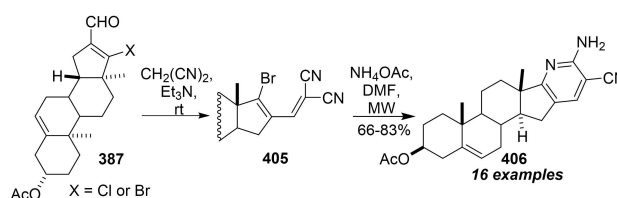
Scheme 108. Synthesis of substituted pyridine derivatives.

Donohoe group presented a Pd-catalyzed excellent approach towards synthesis of substituted pyridine derivatives **399** from β -halovinyl aldehydes **6**, **11** (Scheme 108). Under this study, α -alkenylation with a ketone **2** was carried out using protected β -halovinyl aldehydes **398** in order to get a 1,5-dicarbonyl substituted intermediate, which further undergoes cyclization/double elimination to produce the pyridine derivatives **399**, *via* a one-pot approach (Scheme 109).^[106]

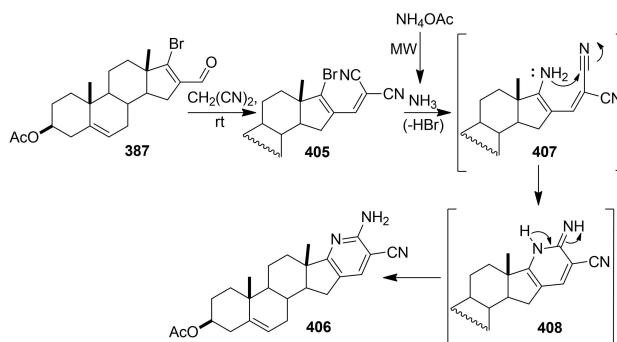
Boruah and co-workers carried out microwave-assisted Knoevenagel reaction of β -halovinyl aldehydes **387** with malononitrile and NH_4OAc to afford 2-aminopyridine derivatives **406** (Scheme 110).^[107] Using this strategy, some novel steroidal and nonsteroidal fused 2-aminopyridines **406** were prepared. Probable mechanism for the reaction is depicted in Scheme 111



Scheme 109. Mechanistic pathway for the synthesis of pyridine derivatives.



Scheme 110. Synthesis of a steroidal fused 2-aminopyridines from β -bromovinyl aldehydes.



Scheme 111. Proposed mechanism for the formation of 2-aminopyridines.

which shows that reaction proceeds through Knoevenagel condensation to furnish **405** followed nucleophilic substitution with NH_3 and subsequent annulation led to generation of 2-aminopyridine fused frameworks **406**.

In another endeavour, Boruah group explored an unorthodox Pd-catalyzed approach to synthesize pyrido[2,3-*d*]pyrimidine derivatives **420**, via coupling of β -bromovinyl aldehydes **11** with 6-amino-1,3-dialkyluracil derivatives **419** (Scheme 112). The reaction was carried out under solvent free conditions and MW irradiation which proceeded through Buchwald–Hartwig cross coupling/cascade imination/cycloaddition reactions (Scheme 113).^[108]

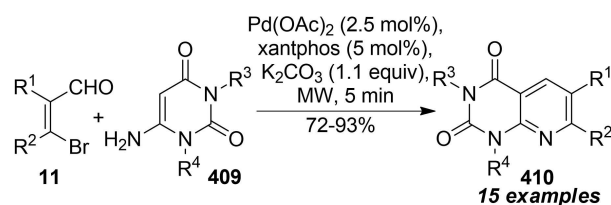
Gogoi and co-workers developed a multi-component cascade methodology to synthesize polysubstituted pyridine derivatives **415** by using β -bromovinyl aldehydes **11**, β -ketoesters/4-hydroxycoumarin **69** and NH_4OAc as the precursors. Interestingly, the reaction proceeded without any additional catalyst or metal salt (Scheme 114)^[109] and strategy was applicable to a large number of β -ketoesters/4-hydroxycoumarins **69** and 1,3-diketones for the synthesis of polycyclic pyridine derivatives **416**. *In vitro* studies of all the synthesized pyridines were carried out for their antiproliferative properties against

human cancer cell lines HeLa, Me180, and ZR751. A proposed reaction mechanism has been depicted in Scheme 115.

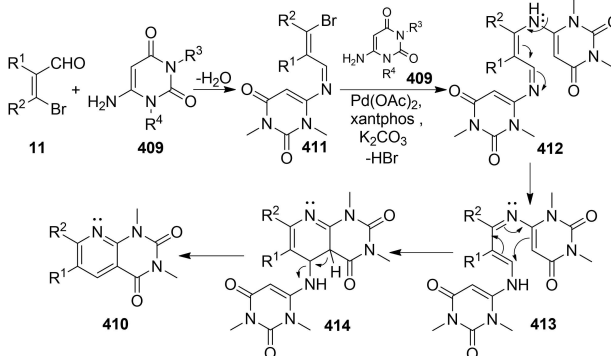
Yao and co-researchers carried out the reaction of β -bromovinyl aldehydes **11** with phenyl acetylenes **17** using PdCl_2 and CuI as a catalyst to obtain functionalized unsymmetrical 1,3-butadiene-3-ynes **425** (Scheme 116).^[110] It was found that functional groups like aldehyde, ester and cyano groups were well tolerated. Furthermore, these 1,3-butadiene-3-ynes **425** furnished the trisubstituted pyridines **427** upon condensation followed by annulation with phenyl hydrazines **426** (Scheme 117).^[110]

The greater geometric instability of hydrazone derivatives **431** over oxime ethers was explored by Harrity and co-workers as a principle element to overcome the reluctance of *Z*-oxime ether azatriene derivatives to undergo electrocyclization reaction for the production of borylated pyridine derivatives and ring-fused analogues. Such hydrazone derivatives **431** allowed access to formerly inaccessible tri- and tetra-substituted 3-borylpyridine derivatives **433** with high yields (Scheme 118).^[111]

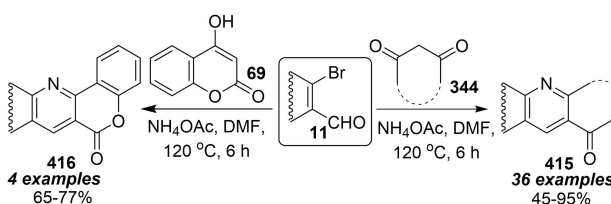
Yao group explored a one-pot Cu-catalyzed multi-component reaction to synthesize disubstituted nicotinonitrile derivatives **444** using β -bromovinyl aldehydes **11**, benzoylacetonitriles



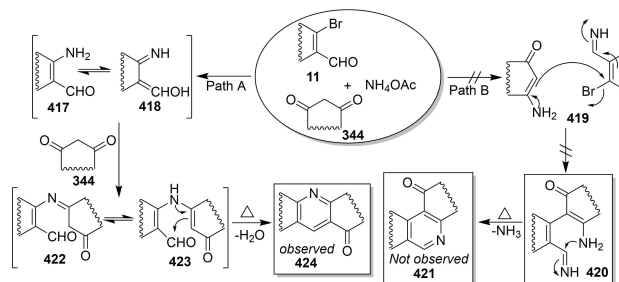
Scheme 112. Synthesis of pyrido[2,3-*d*]pyrimidine derivatives.



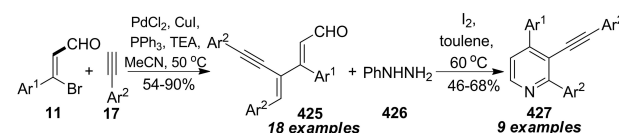
Scheme 113. Proposed mechanism for the formation of pyrido[2,3-*d*]pyrimidines.



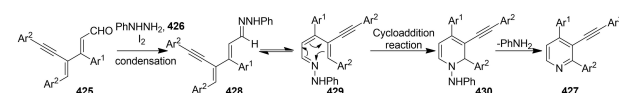
Scheme 114. Synthesis of polysubstituted pyridine derivatives.



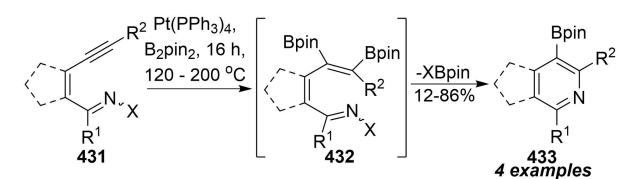
Scheme 115. Reaction mechanism for the formation of pyridines.



Scheme 116. Formation of trisubstituted pyridines.



Scheme 117. Proposed mechanism for synthesizing pyridine derivatives.



Scheme 118. One-pot diboration-electrocyclization of oximes and hydrazones.

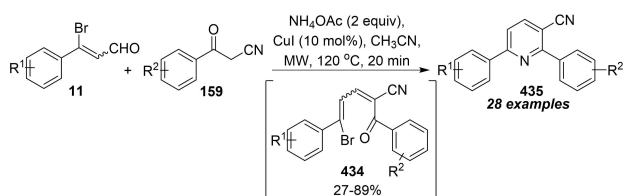
161, and NH_4OAc (Scheme 119).^[112] Knoevenagel-type condensation reaction of β -bromovinyl aldehydes **11** and benzoylacetone nitriles **161** afforded the δ -bromo-2,4-dienones **443** having intendedly installed functional groups which reacted with ammonia generated *in situ* to yield the corresponding azatriene derivatives. These azatriene derivatives were transformed into trisubstituted pyridine derivatives **435** via 6π -azaelectrocyclization and aromatization process (Scheme 120).^[112]

4.3.3. Synthesis of Pyrimidine Derivatives

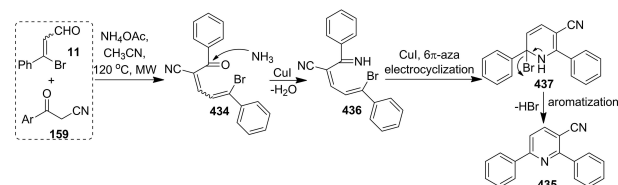
Lin and co-workers prepared a library of pyrimidine derivatives **439** via cyclocondensation of β -bromovinyl aldehydes **11** with different amidine hydrochlorides **438** in presence of Et_3N with excellent yields (74–95 %) (Scheme 121).^[113]

Kirsch group performed the condensation reaction between 3-amino(benzo)thiophene carboxylate **440** and chloroformamide hydrochloride with a focus on synthesizing 2-aminothieno[3,2-*d*]pyrimidin-4-one derivatives **441** in a single step only (Scheme 122).^[114]

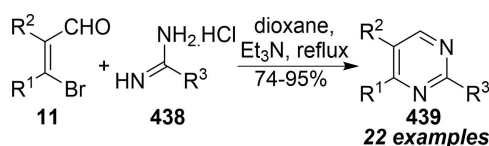
Similarly, Gogoi and co-workers explored a Pd-catalyzed procedure for synthesizing fused steroidal and non-steroidal



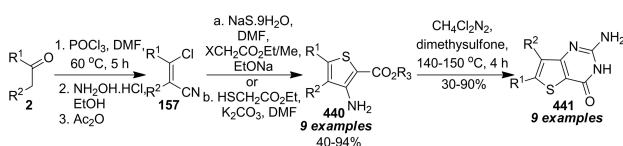
Scheme 119. Synthesis of disubstituted nicotinonitrile derivatives.



Scheme 120. Proposed reaction mechanism for the formation of nicotinonitriles.



Scheme 121. Synthesis of pyrimidine derivatives.



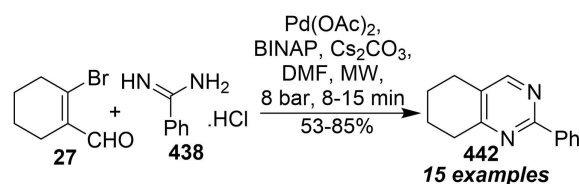
Scheme 122. Synthesis of 2-aminothieno[3,2-*d*]pyrimidin-4-one derivatives.

pyrimidine derivatives **442** under microwave irradiation from β -halovinyl aldehydes **27** (Scheme 123).^[115] This strategy was further used to synthesize several novel steroidal pyrimidines. Mechanistic pathway for the catalytic cycle has been depicted in Scheme 124.

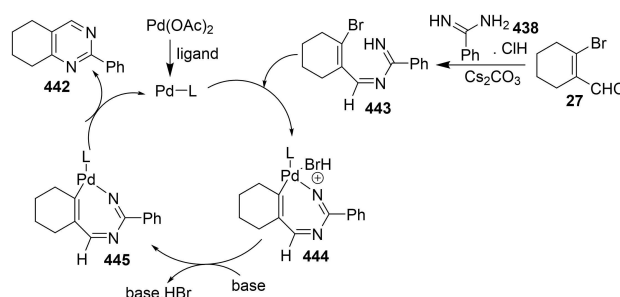
Volkova and co-workers reported a practical, and facile strategy to prepare functionalized 2-aminopyrimidine derivatives **446** via reaction of β -chlorovinyl aldehydes **11**, **27** with amidines or guanidines **438**. Many ketones were effectively modified into pyrimidines in presence of potassium carbonate through a two-step strategy via Vilsmeier–Haack reaction which then followed a condensation reaction with guanidines **438** (Scheme 125).^[116] This strategy offered advantages like operational simplicity, economically accessible reagents, and wide functional-group tolerance. The synthetic value of this method was exemplified by the effective synthesis of steroidal pyrimidine derivatives **446** and a precursor of the antitumor agents Imatinib and Mocetinostat.

4.3.4. Synthesis of Pyran Derivatives

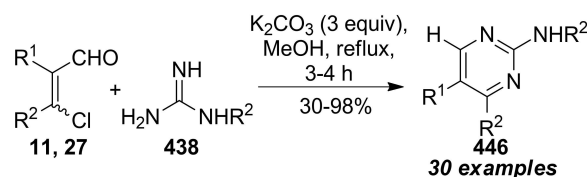
Ma and co-workers carried out oxidative condensation of β -bromovinyl aldehydes **11** with 1,3-dicarbonyl compounds **344** using N-heterocyclic carbenes as a catalysis for the selective synthesis of either 2*H*-pyran-2-one **449** or chiral dihydropyr-



Scheme 123. Synthesis of steroidal and non-steroidal pyrimidines via Pd-catalyzed reaction.



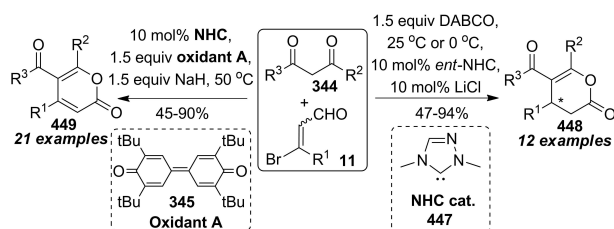
Scheme 124. Mechanistic pathway for the catalytic cycle.



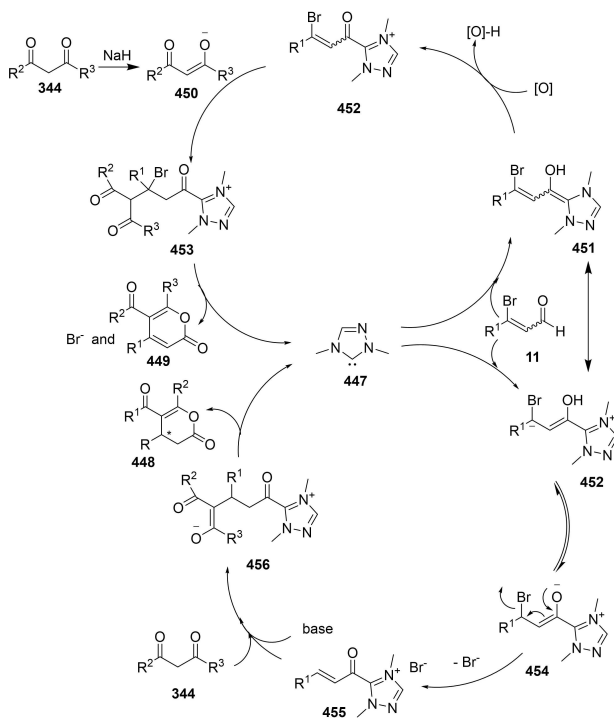
Scheme 125. Condensation of β -chlorovinyl aldehydes and guanidines for synthesizing 2-aminopyrimidines.

anone derivatives **448** (Scheme 126).^[117] It was noted that the oxidative conversion of β -bromovinyl aldehydes **11** using NHC catalyst can be controlled in a very precise manner to proceed via two pathways, i.e. elimination of reducible β -bromide or by an external oxidant **345**, permitting the selective generation of two types of unsaturated acyl azolium intermediates **452** and **455** which governed the fate of reaction (Scheme 127).^[117]

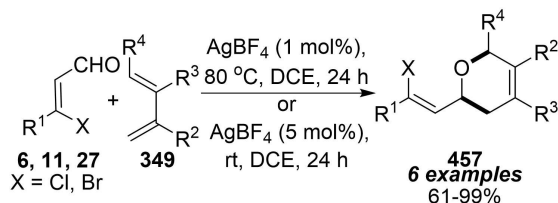
Lua and co-workers carried out chemoselective oxa-Diels–Alder reaction between electronically neutral 1,3-dienes **349**



Scheme 126. Selective synthesis of either 2H-pyran-2-ones or chiral dihydropyranone derivatives.



Scheme 127. Proposed reaction mechanism for the synthesis of 2H-pyran-2-ones or dihydropyranones.



Scheme 128. Reaction between electrically neutral dienes and β -halovinyl aldehydes.

and different β -halovinyl aldehydes **6**, **11**, **27** in presence of silver tetrafluoroborate (AgBF_4) as a catalyst (Scheme 128).^[118]

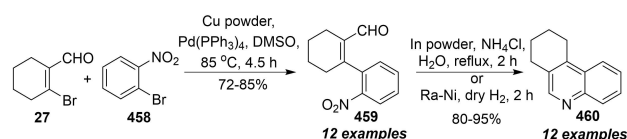
The strategy was found to exhibit high functional group tolerance. Heteroatoms present at the β -position of vinyl aldehydes were found to efficiently enhance the reactivity of the substrates even with heterocyclic aldehydes that were earlier supposed to be unreactive towards the oxa-Diels–Alder reaction. Oxa-Diels–Alder reaction between β -halovinyl aldehydes **5**, **11** and 1,3-dienes **349** was found to exhibit high chemo- and regio- selectivity at room temperature.

4.3.5. Synthesis of Quinoline Derivatives

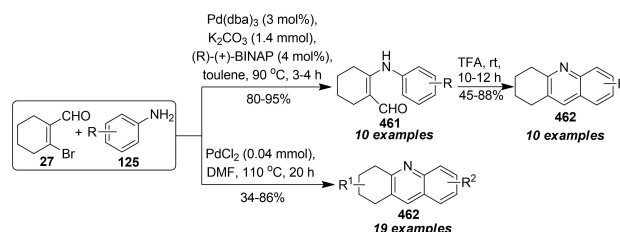
Banwell and co-workers carried out the Pd/Cu-assisted Ullmann cross-coupling between easily accessible β -bromovinyl aldehydes **27** and 1-bromo-2-nitrobenzene **458** to furnish the β -(*o*-nitrophenyl)acrylaldehydes **459**, which further underwent reductive cyclization to produce the annulated quinoline derivatives **460** upon exposing to indium/ NH_4Cl or Raney-nickel/ H_2 (Scheme 129).^[119] Similar kind of cross-coupling of 2-bromoacetanilide with β -bromovinyl aldehydes afforded N-(2-(2-formylcyclobut-1-en-1-yl)phenyl) acetamides that upon K_2CO_3 -mediated cyclization yielded the similar kind of quinoline derivatives.

Ray and co-workers carried out a Pd-catalyzed chemoselective amination of β -bromovinyl aldehydes **27** with aromatic amines **125** and a subsequent acid catalyzed intramolecular cyclization yielded the polycyclic quinoline derivatives **462** as depicted in Scheme 130.^[120a] In a closely related approach, Choa group also carried out the Pd-catalyzed cascade cyclization of β -bromovinyl aldehydes **27** with arylamines **125** in DMF as a solvent at 110 °C to furnish the similar quinoline derivatives **462** (Scheme 130).^[120b]

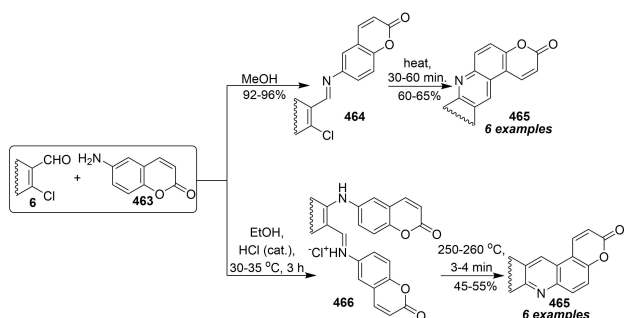
Kar group performed the thermolysis of enaminoimine hydrochlorides to synthesize 3H-pyrano[3,2-*f*]quinolin-3-ones **465**, 3H-acenaphtho[1,2-*b*]pyrano-[3,2-*f*]quinolin-3-ones, and 3H-benzo[*h*]pyrano[3,2-*a*]acridin-3-ones (Scheme 131).^[121a] Similarly, Patra *et al.* conducted thermolysis of suitable chlorovinyl



Scheme 129. In/ NH_4Cl and Ra–Ni/ H_2 catalysed synthesis of quinolines via reductive cyclization.



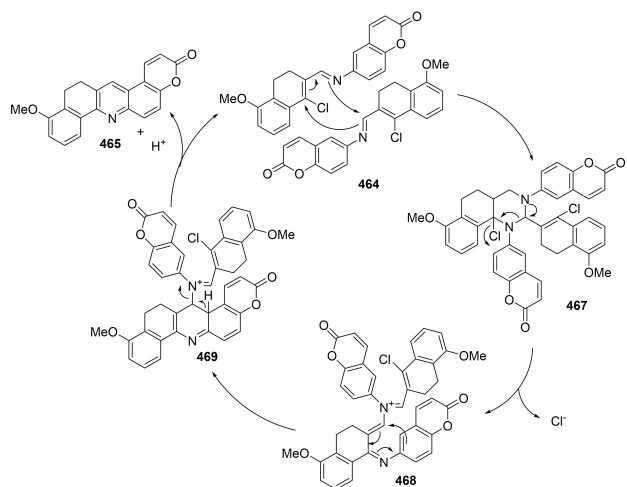
Scheme 130. Synthesis of polycyclic quinoline derivatives.



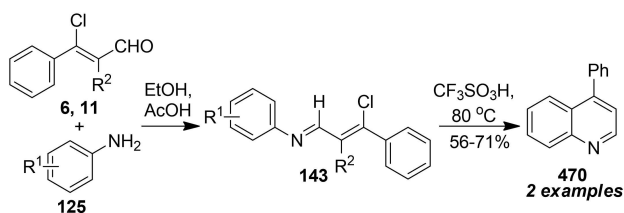
Scheme 131. Formation of pyranoquinolin-3-ones via thermolysis.

imines **466** at 250–260 °C for the synthesis of 3*H*-pyrano[3,2-*f*]quinolin-3-ones **465** and 3*H*-benzo[*h*]pyrano[3,2-*a*]acridin-3-ones. The chlorovinyl imines **464**, **466** were generated via condensation of suitable β -chlorovinyl aldehydes **6** with 6-aminocoumarins **463** in MeOH (Scheme 131).^[121b] It was observed that in alkaline medium, these compounds exhibited blue fluorescence. A possible mechanistic pathway is depicted in Scheme 132.

Klumpp and co-workers prepared a library of vinylogous imine derivatives **143** via AcOH-promoted condensation of different anilines **125** and β -halovinyl aldehydes **6**, **11**. Further exposure of **143** to superacidic media resulted in formation of 4-aryl quinoline derivatives **470** (Scheme 133).^[122] Mechanism proposed for the conversion involved the cyclization of



Scheme 132. Proposed mechanism for the formation of pyranoquinolin-3-ones.



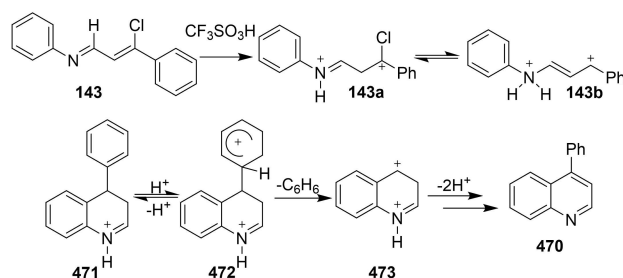
Scheme 133. Synthesis of quinoline derivatives.

dicationic super electrophilic intermediates **143b** to furnish quinoline ring (Scheme 134).^[122]

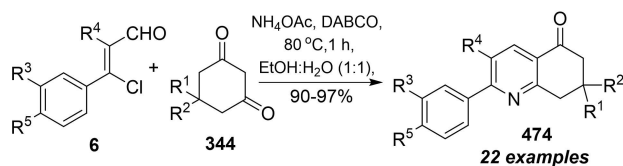
Dhara and co-workers explored a DABCO-catalyzed metal-free domino methodology for the facile synthesis of dihydro-6*H*-quinolin-5-one derivatives **474**. This strategy provided a convenient route for synthesizing pyridine frameworks from readily available β -chlorovinyl aldehydes **6**, 1,3-diketones **344**, and ammonium acetate in ethanol:water (1:1) under environment-friendly conditions (Scheme 135).^[123] It was found that different type of cyclic and acyclic β -chlorovinyl aldehydes **6** can be employed for the synthesis of a wide range of dihydro-6*H*-quinolin-5-ones **344**. A reliable mechanism was proposed for this domino reaction by isolating the intermediate molecules (Scheme 136). With the help of spectral and single crystal XRD studies, structure of the intermediates was estimated. Most of these synthesized dihydro-6*H*-quinolin-5-ones were found to show cytotoxicity towards the HeLa cell lines in MTT assays.

Hayashi and co-workers carried out a one-pot synthesis of substituted quinolines **488** via domino reaction of *o*-alken-yals **224** and dicyanoalkenes **487**. Two methods were introduced: first one was catalyzed by chiral diphenylprolinol silyl ether, and the other one by di(2-ethyl)hexylamine, in combination with *p*-nitrophenol (Scheme 137).^[124] A wide range of dicyanoalkenes **487** were compatible during this eco-friendly approach for preparing substituted quinoline derivatives **488** since the catalysts used were secondary amines, and water was the only by-product. The mechanism of this reaction is depicted in Scheme 138.

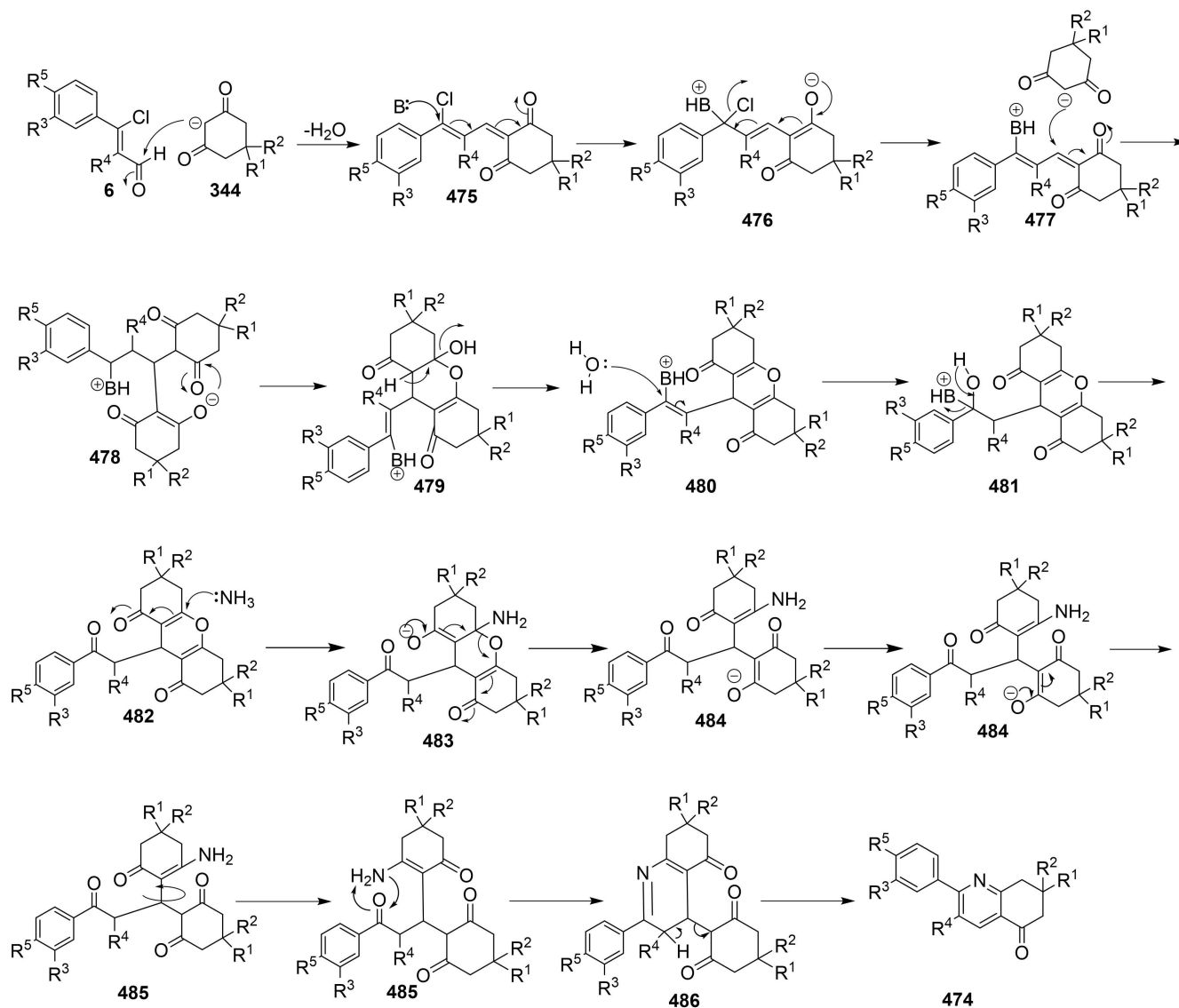
Samanta group also reported a one-pot, AcOH-promoted tandem aza-Michael-aldol methodology for synthesizing pyrrolo[1,2-*a*]quinoline derivatives **497** (tricyclic to pentacyclic scaffolds) with the formation of both pyrrole as well as quinoline ring (Scheme 139).^[125] This strategy involved the constitution of two C–N bonds and one C–C bond in the pyrrolo[1,2-*a*]quinoline framework **497** that were formed subsequently under transition-metal-free conditions. A ketorolac drug analog was synthesized using this strategy, and one of the



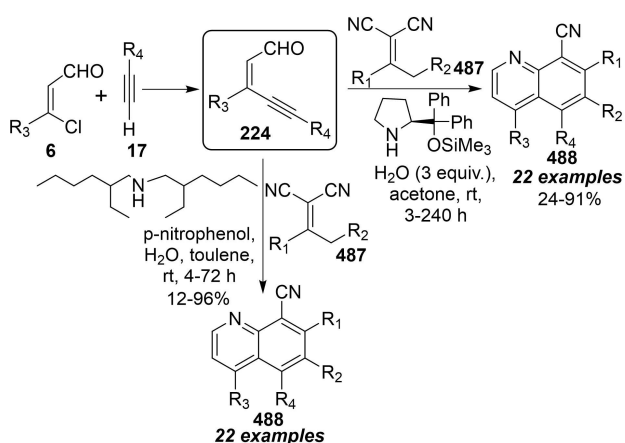
Scheme 134. Proposed reaction mechanism for quinoline synthesis.



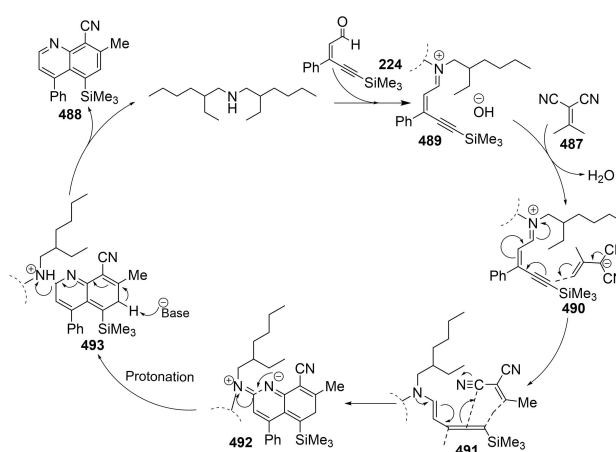
Scheme 135. Synthesis of dihydro-6*H*-quinolin-5-one derivatives.



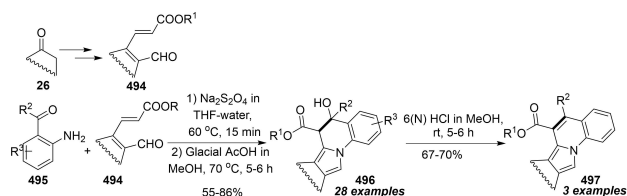
Scheme 136. Probable mechanistic pathway for synthesizing dihydro-6H-quinolin-5-ones.



Scheme 137. Reaction between dicyanoalkene and enynals.

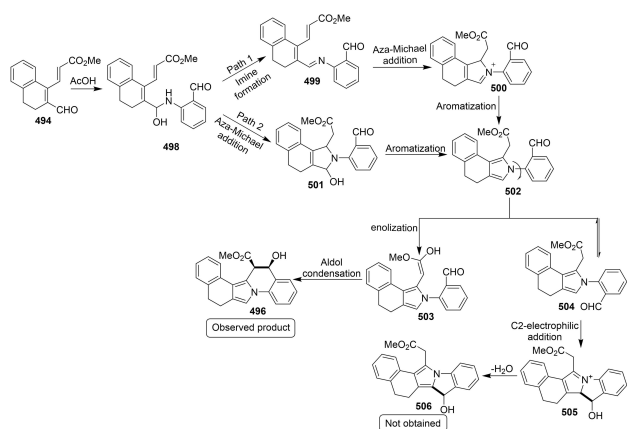


Scheme 138. Mechanism for the formation of quinolines from enynals.

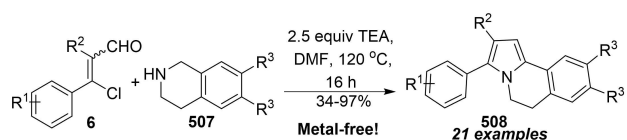


Scheme 139. Synthesis of pyrrolo[1,2-*a*]quinoline derivatives *via* tandem-aza-Michael aldol reaction.

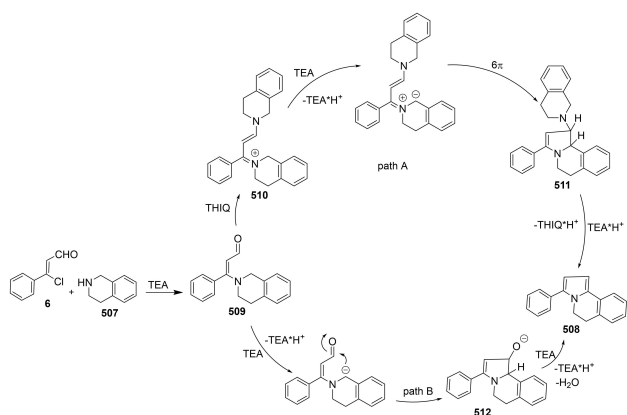
manufactured tricyclic pyrrolo[1,2-*a*]quinoline fluorophores **497** was used for the detection of highly toxic picric acid through the fluorescence quenching effect (Scheme 140).^[125]



Scheme 140. Mechanism for the formation of benzo-isindolo[2,1-*a*]quinolin-carboxylates.



Scheme 141. Formation of pyrrolo[2,1-*a*]isoquinoline derivatives.



Scheme 142. Proposed reaction mechanism.

4.3.6. Synthesis of Isoquinoline Derivatives

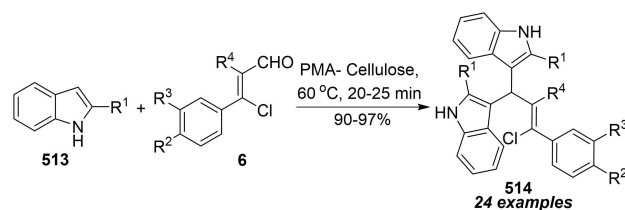
Lin group reported a one-pot base-promoted intermolecular cyclization between substituted β -aryl(heteroaryl)- β -chlorovinyl aldehydes **6** and tetrahydroisoquinoline derivatives **507**. This strategy provided a simple and efficient synthesis of pyrrolo[2,1-*a*]isoquinoline derivatives **508** (Scheme 141) with good to excellent yields (up to 97%). Mechanism for this synthesis has been presented in Scheme 142.^[126]

4.3.7. Synthesis of Indole and Isoindole Derivatives

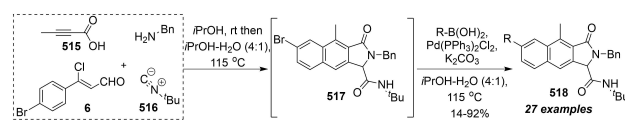
Dhara and co-workers synthesized a series of bis(indolyl)methanes **514** using β -chloro-vinylaldehydes **6** as a precursor which emerged excellent fluorophore and showed prominent naked eye sensitivity towards Cu^{2+} ions. This environment-friendly one-pot approach was developed by using PMA-cellulose as a reusable solid acid support/catalyst under solvent free reaction conditions. BIM molecules **514** were obtained in excellent yields in short time (Scheme 143).^[127]

Peshkov group explored β -chlorovinyl aldehydes and generated a one-pot strategy to provide an easy access to isoindolinone frameworks **518** in a diversity-oriented fashion *via* a four-component Ugi reaction followed by an intramolecular Diels-Alder reaction and HCl-elimination cascade. The scope of this methodology was exhibited with respect to all four components and a comparative study between the one-pot vs sequential approaches was also carried out (Scheme 144).^[128] The authors also investigated the possibility of late-stage functionalization *via* Suzuki coupling.

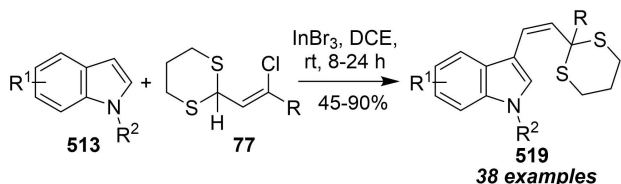
Tang group realised a protocol for the C-H alkenylation of N-H indole derivatives **513** with β -chlorovinyl dithianes **77** to provide alkenyl indole derivatives **519** *via* dual 1,3-sulfur rearrangements (Scheme 145).^[129] This alkenylation method was compatible to synthesize a variety of vinyl indole derivatives **519** in a selective manner with moderate to excellent yields. Mechanism for this reaction is shown in Scheme 146.



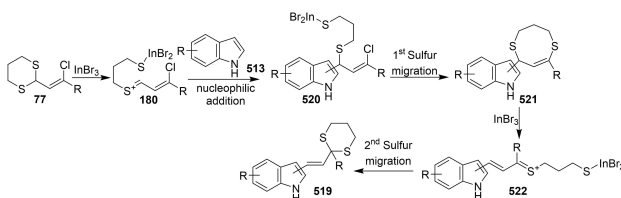
Scheme 143. Synthesis of BIM derivatives using β -chloro-vinylaldehydes.



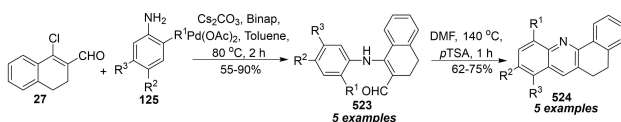
Scheme 144. Synthesis of isoindolinone derivatives *via* four component Ugi-reaction.



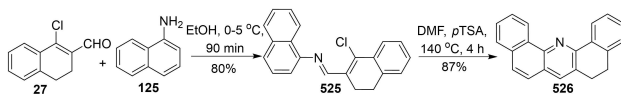
Scheme 145. C–H alkenylation of indoles.



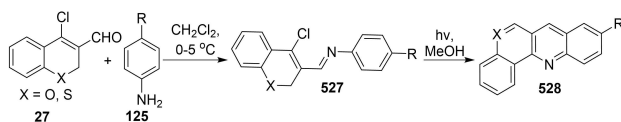
Scheme 146. Reaction mechanism for C–H alkenylation of indoles.



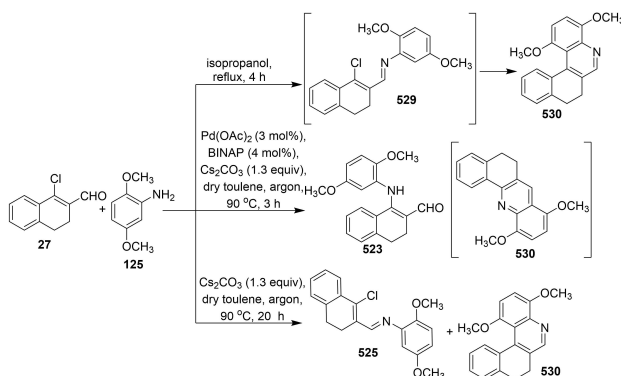
Scheme 147. Synthesis of 5,6-dihydro-benz[c]acridine derivatives.



Scheme 148. Synthesis of 5,6-dihydrobenz[c, h]acridines.



Scheme 149. Synthesis of benzopyrano[4,3-b]quinolines.



Scheme 150. Synthesis of 7,8-dihydrobenz[k]phenanthridines.

4.3.8. Synthesis of Acridines and Phenanthrolines

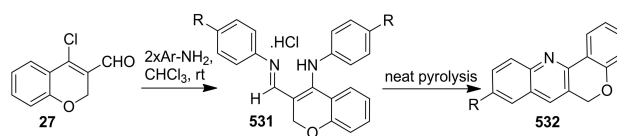
Kabilan and co-workers carried out the synthesis of 5,6-dihydrobenz[c]acridine derivatives **524** via reaction of β -chlorovinylaldehydes; 1-chloro-3,4-dihydro-2-naphthaldehyde **27** with aromatic amines **125** under three different conditions:

- Thermolysis of 1-chlorovinyl-(N-aryl)imine derivatives synthesized from 1-chloro-3,4-dihydro-2-naphthaldehyde.
- Acid catalyzed cyclization of 1-(N-aryl)amino-3,4-dihydro-2-naphthaldehyde derivatives.
- Thermolysis of N-arylaminoimine hydrochloride derivatives derived from 1-chloro-3,4-dihydro-2-naphthaldehyde in DMF.

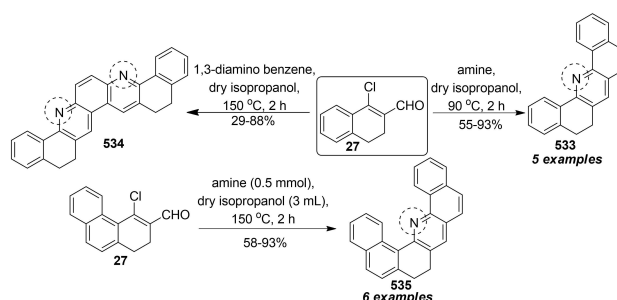
Interestingly, all these three approaches solely furnished only 5,6-dihydrobenz[c]acridine derivatives **524** and not the isomeric 7,8-dihydrobenzo[k]phenanthridine derivatives (Schemes 147–151).^[130] The structural studies were completed by using detailed NMR spectral analysis and single crystal XRD.

Prim and co-workers synthesized a new library of acridine and phenanthroline derivatives **533–535** starting with β -chlorovinyl aldehydes **27** and different aniline derivatives permitting the insertion of valuable substituents, like nitro, ketone, or amino groups in the heterocyclic core. Structures of acridine and phenanthroline derivatives along with the presence of partially hydrogenated rings and their pivotal influence on the overall shape of the acridine-based frameworks **533**, **535** was confirmed with the help of X-ray analysis (Scheme 152).^[131] The helical behavior of acridines was investigated through ¹H NMR. Comparison of UV data of different frameworks and influence of number of partially hydrogenated rings was also investigated.

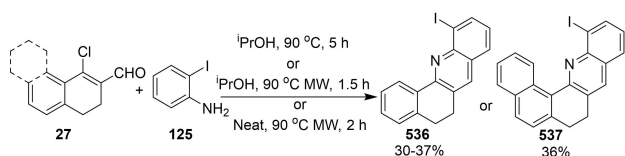
In another study, Prim and co-workers synthesized substituted dihydrobenzo- and dihydronaphtho- acridine derivatives **536–537** in two key steps (Scheme 153).^[132] A diverse range of carbon-based substituents like vinyl, aryl, alkynyl fragments were installed *via* Pd-catalyzed coupling reactions. By using Cu-promoted C–N bond formation strategy, the molecular diversity



Scheme 151. Synthesis of benzopyrano[4,3-b]quinolines.



Scheme 152. Synthesis of dihydroacridines and phenanthroline derivatives.



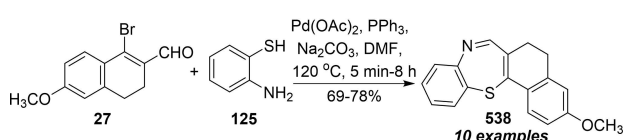
Scheme 153. Preparation of iodoacridine derivatives.

was extended to the install the alkylamino chains. Probable access to quinolinium salts was also reported.

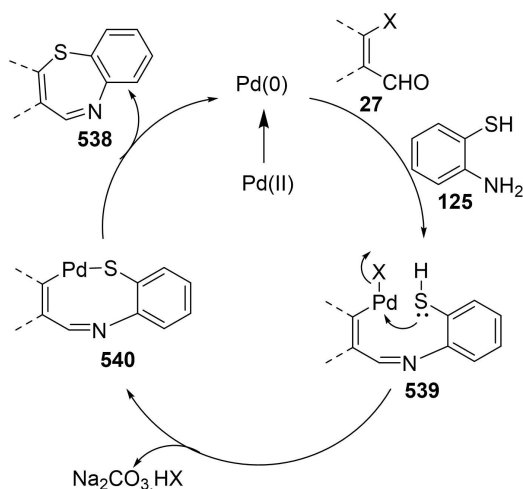
4.4. Formation of Seven-membered Heterocycles

4.4.1. Synthesis of Benzothiazepines

Boruah group formulated a library of steroid/nonsteroid fused benzo[*b*][1,4]thiazepines and 2-arylsubstituted benzo[*b*][1,4]thiazepines **538** under Pd(OAc)₂ catalyzed reaction of steroidal/nonsteroidal β-halovinyl aldehydes **27** and 2-aminothiophenols **125** using DMF as a solvent and under heating conditions (Scheme 154).^[133] Mechanism for the formation of benzothiazepines is depicted in Scheme 155.



Scheme 154. Pd-catalyzed generation of benzo[*b*][1,4]thiazepines.



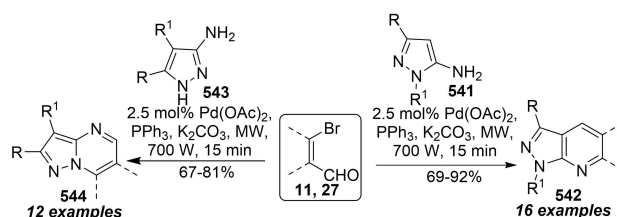
Scheme 155. Probable reaction mechanism of Pd-mediated synthesis of benzothiazepine derivatives.

5. Formation of Fused Heterocycles

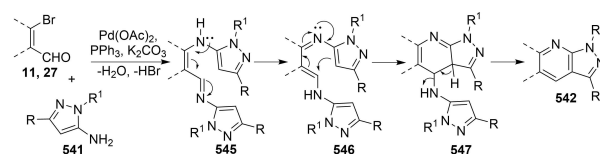
5.1. Synthesis of Pyrazole Fused Heterocycles

Gogoi and co-workers developed a facile and effective method for the synthesis of pyrazole fused heterocycles **542**, **544** through Pd-catalyzed reaction of β-halovinyl/aryl aldehydes **11**, **27** and 5-aminopyrazole/3-aminopyrazole derivatives **541**, **543** under microwave irradiation and solvent free conditions (Scheme 156).^[134] Using this methodology a diverse range of substituted pyrazolo[3,4-*b*]pyridine, pyrazolo[3,4-*b*]quinoline, pyrazolo[1,5-*a*]pyrimidine and pyrazolo[1,5-*a*]quinazoline derivatives **542**, **544** were synthesized. These pyrazole fused scaffolds exhibited *in vitro* cytotoxic activities which were almost comparable to doxorubicin against the cervical HeLa cancer cell lines and prostate DU 205 cancer cell lines. Mechanism for the above mentioned strategy is depicted in Scheme 157.

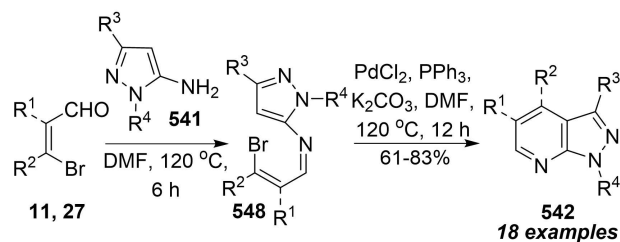
Similarly, Boruah and co-workers also developed a Pd-catalysed excellent approach for the synthesis of 1,3,4-trisubstituted pyrazolo[3,4-*b*]pyridines, 3*H*-pyrazolo[3,4-*c*]isoquinolines and 3*H*-pyrazolo[4,3-*f*][1,7]naphthyridine derivatives **542** through intramolecular Heck reaction of imines **548** afforded from the condensation of β-halovinyl aldehydes **11**, **27** with 5-aminopyrazole derivatives **541** (Scheme 158).^[135] In presence of Pd(OAc)₂ as a catalyst and xantphos as ligand, the intramolecular C–C bond formation furnished the pyrazolopyr-



Scheme 156. Synthesis of various pyrazole fused heterocycles.



Scheme 157. Proposed mechanism for the formation of pyrazolo[3,4-*b*]pyridine derivatives.



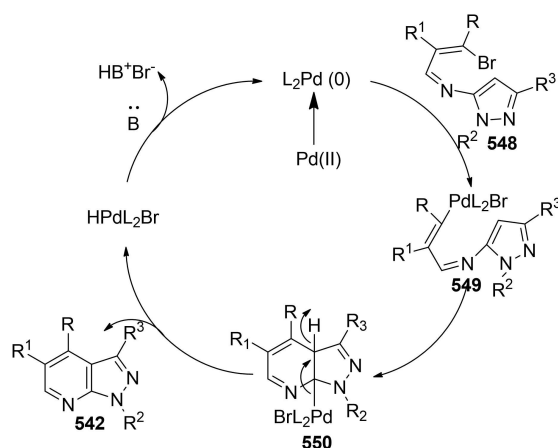
Scheme 158. Synthesis of pyrazolo[3,4-*b*]pyridines *via* intramolecular Heck reaction.

idines **542** in 61–83% yields. The mechanism for the formation of pyrazolo[3,4-*b*]pyridines **542** is depicted in Scheme 159.

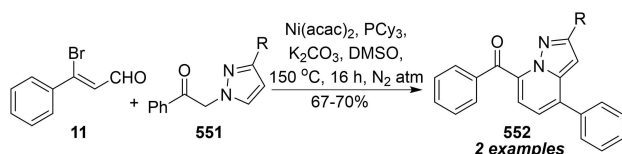
Kumar and co-workers unveiled a facile procedure for the generation of pyrazolo[5,1-*a*]isoquinolines **552** via reaction of β -bromovinyl aldehydes **11** with 1-aryl-2-(1*H*-pyrazol-1-yl)ethan-1-one derivatives **551** using Ni(acac)₂ as a catalyst (Scheme 160).^[136] This overall transformation involved tandem Knoevenagel condensation and intramolecular direct arylation by activation of C₅–H bond of the pyrazole ring (Scheme 161). By using this approach, a series of 27 drug-like aroyl-substituted pyrazolo[5,1-*a*]isoquinoline derivatives **552** were synthesized with 67–70% yields.

5.2. Synthesis of Imidazole Fused Heterocycles

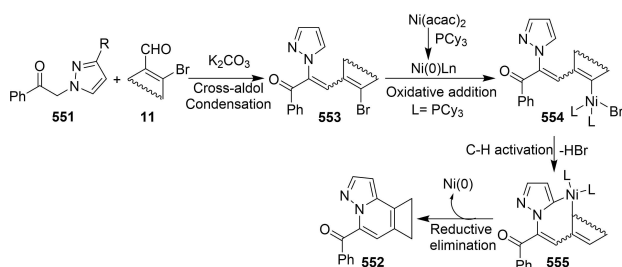
Pandey group reported the transformation of chromeno-annulated imidazo[1,2-*a*]pyridines **557** from β -bromovinyl aldehydes **11**. A one-pot reaction between 2-amino-1-(2-ethoxy-2-



Scheme 159. Reaction mechanism for the formation of pyrazolo[3,4-*b*]pyridines.



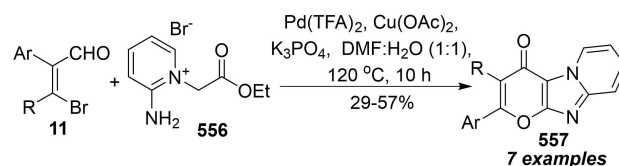
Scheme 160. Ni-assisted synthesis of pyrazolo[5,1-*a*]pyridines.



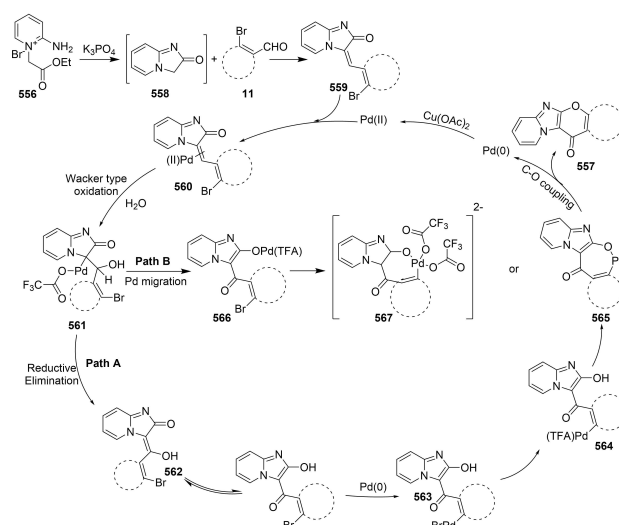
Scheme 161. Proposed mechanism for the formation of pyrazolo[5,1-*a*]pyridines.

oxoethyl)pyridinium salts **556** and β -bromovinyl aldehydes **11** under the catalysis of Pd(TFA)₂ and oxidant Cu(OAc)₂ directly furnished the chromeno-annulated imidazo[1,2-*a*]pyridine derivatives **557** (Scheme 162).^[137] This overall strategy comprised of tandem base-mediated amidation and Knoevenagel condensation, which further followed Pd-catalyzed Wacker type oxidation and an intramolecular C–O coupling reaction (Scheme 163). Facile nature of the process, functional group compatibility and good yields were the characteristic features of this strategy. This tandem reaction was also applicable for the synthesis of pyrano-fused imidazo[1,2-*a*]pyridine derivatives using β -bromovinyl aldehydes **11** as the precursor.

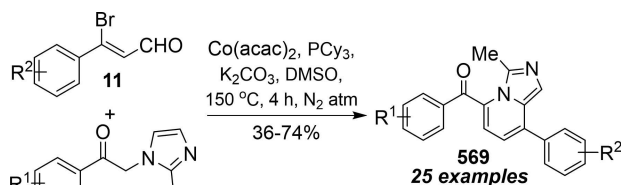
After successful synthesis of pyrazolo[5,1-*a*]isoquinolines **552**; Kumar group also developed an efficient Co-catalyzed tandem one-pot strategy for the synthesis of polysubstituted imidazo-N-fused heterocycles **569**. A Base-promoted Knoevenagel condensation of β -bromovinyl aldehydes **11** and 2-(2-methyl-1*H*-imidazol-1-yl)-1-phenylethanone furnished the cross Aldol product **570** which upon cobalt-catalyzed direct alkenylation afforded the imidazo[1,5-*a*]pyridines and imidazo[1,5-*a*]isoquinoline derivatives **569** (Scheme 164).^[138] This strategy exhibited broad substrate scope and was also amenable to gram scale synthesis furnishing the products in 39–74% yields. A proposed mechanism for the formation of imidazo[1,5-*a*]pyridines has been depicted in Scheme 165.



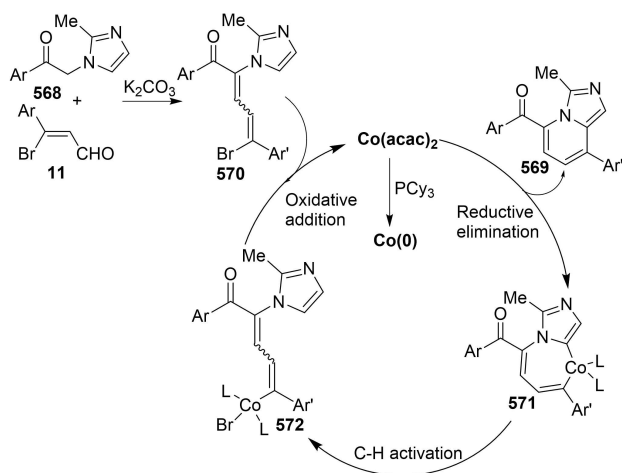
Scheme 162. One-pot synthesis of chromeno-annulated imidazo[1,2-*a*]pyridines.



Scheme 163. Plausible reaction mechanism for the synthesis of chromeno-annulated imidazo[1,2-*a*]pyridines.



Scheme 164. Preparation of the imidazo[1,5-*a*]pyridine skeleton via Knoevenagel condensation.

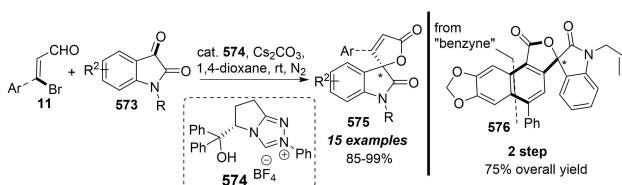


Scheme 165. Proposed reaction mechanism for the synthesis of imidazo[1,5-*a*]pyridines.

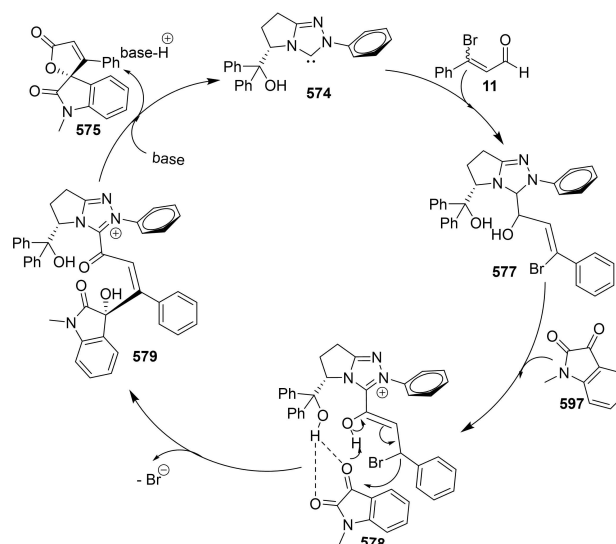
6. Synthesis of Spirooxindoles

Ma and co-workers explored chiral N-heterocyclic carbene **574** as a catalyst and performed an asymmetric formal (3+2) cyclization reaction between β -bromovinyl aldehydes **11** and isatins **573** to furnish a diverse range of chiral spirooxindole-butenolide derivatives **575** (Scheme 166).^[139] The detailed mechanism for the formation of spirooxindole-butenolide derivatives **575** is presented in Scheme 167.

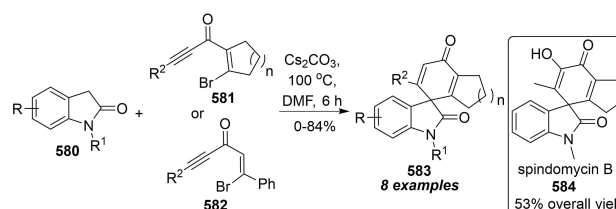
Mehta and co-workers developed an efficient, one-pot transition metal-free approach for the synthesis of spiro[cyclohexa[2,5]diene-1,3'-indoline]-2',4-dione derivatives **583**. Domino Michael- S_NAr or Ad_NE substitution strategy initiated the spiroannulation of oxindole derivatives **580** with *ortho*-bromoaryl ynone; β -bromoalkenyl ynone and β -bromoalkenyl enone derivatives **581–582** (Scheme 168).^[140] Mechanism for this strategy has been depicted in Scheme 169. A short



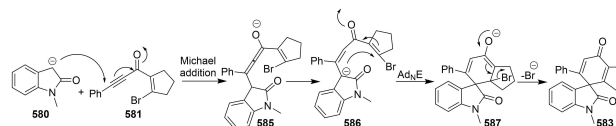
Scheme 166. NHC-catalyzed formation of chiral spirooxindole-butenolides.



Scheme 167. Probable reaction mechanism.



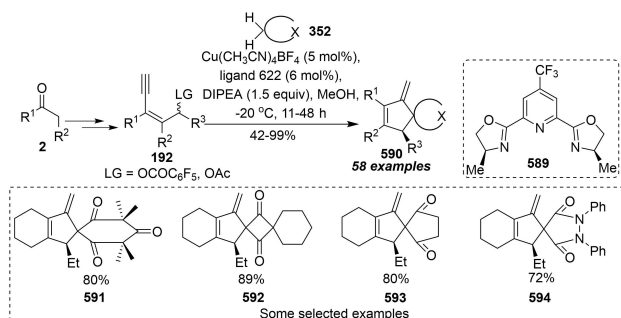
Scheme 168. Michael- Ad_NE reaction of oxindoles with β -bromoalkenylnones.



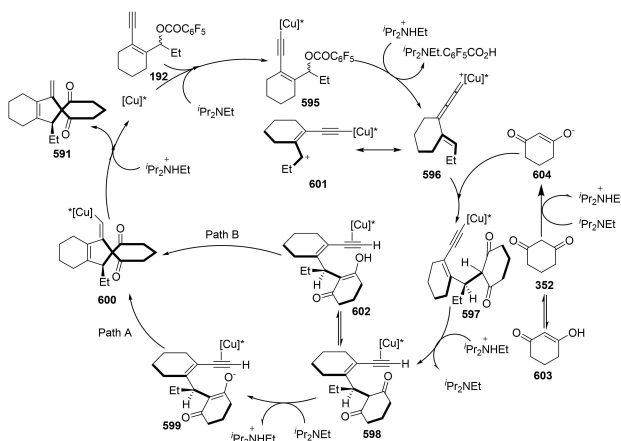
Scheme 169. Proposed reaction mechanism.

synthesis of tetracyclic alkaloid spindomycin B **584** was also achieved as an application part.

Xu and co-workers were the first who carried out the copper-catalyzed enantioselective [4+1] annulation of yne-allylic esters **192** with 1,3-dicarbonyl compounds **352** using an effective remote stereo-control methodology. The remote ϵ regioselective nucleophilic substitution was carried out by using an unorthodox chiral copper-vinylvinylidene species from the new C_4 synthon yne-allylic esters **192** (Scheme 170).^[141] Consequently, diversified spirocycles **590** were furnished having huge scope and excellent levels of enantio-, chemo-, and regioselectivity. The detailed mechanistic studies suggested an yne-allylic substitution and Conia-ene cascade pathway on the remote stereochemical induction progress (Scheme 171).



Scheme 170. Copper-catalyzed remote asymmetric [4 + 1] annulation of yne-allylic esters with 1,3-dicarbonyl compounds.

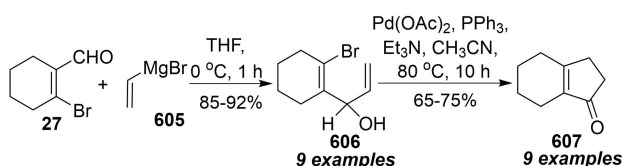


Scheme 171. Probable reaction mechanism.

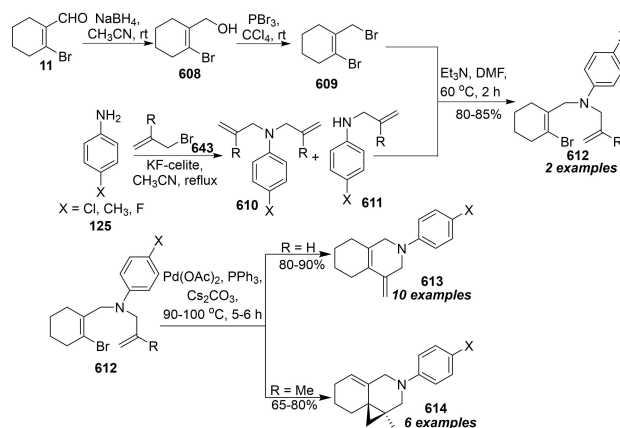
7. Miscellaneous Reactions of β -halovinyl Aldehydes

Ray and co-workers developed a facile and efficient strategy for the synthesis of substituted cyclopentenone derivatives **607** via reaction of cyclic β -bromovinyl aldehydes **27** with Grignard reagent followed by Pd-catalyzed intramolecular 5-*endo-trig* oxidative cyclization (Scheme 172).^[142]

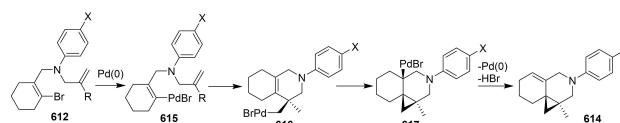
Ray group also carried out a Pd-catalyzed intramolecular cyclization/cyclopropanation for the conversion of a large number of substituted cyclic *N*-aryl allyl/methallyl amine derivatives **612** very effectively and particularly to the corresponding fused tetrahydropyridine/cyclopropane-fused isoquinolines **613**, **614** through β -hydrogen elimination or a domino sequence (Scheme 173).^[143] Proposed mechanism for the reaction is shown in Scheme 174.



Scheme 172. Pd-catalyzed intramolecular 5-*endo-trig* cyclization for the synthesis of cyclopentenones.



Scheme 173. Synthesis of tetrahydropyridine/cyclopropane-fused isoquinolines via Pd-catalyzed intramolecular cyclization.



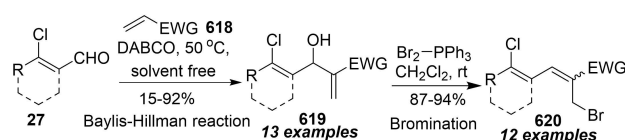
Scheme 174. Mechanism for the Pd(0)-catalyzed cyclopropanation.

Zhong and co-workers explored β -chlorovinyl aldehydes **27** for the first time for DABCO-assisted Morita-Baylis-Hillman (MBH) reaction under sonochemical solvent-free conditions and obtained MBH allylic alcohols **619** in 15–92% yields. The β -chlorovinyl aldehydes **27** were in turn prepared via bis(trichloromethyl) carbonate (BTC)/DMF-mediated Vilsmeier-Haack reaction of ketones (Scheme 175).^[144] $\text{Br}_2\text{-Ph}_3\text{P}$ system was used for the stereoselective bromination of MBH adducts under milder conditions in 87–94% yields.

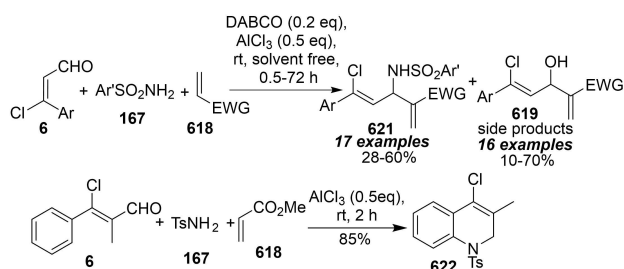
In another study, Zhong group performed DABCO/ AlCl_3 assisted aza-Baylis-Hillman reaction of β -chlorovinyl aldehydes **6**, benzenesulfonamides **167** and different activated alkenes to furnish Aza-adducts **622** under solvent-free conditions (Scheme 176).^[145] Mechanistic pathway for the formation of quinoline frameworks is depicted in Scheme 177.

Ray group developed another excellent approach for the synthesis of 9-fluorenylidene derivatives via a Pd-catalyzed domino intermolecular Suzuki reaction of **626** and 2-bromo phenylboronic acid **85** which then followed intramolecular Heck coupling under milder reaction conditions (Scheme 178).^[146] The key precursor **626** was prepared from β -bromovinyl aldehydes **27** via Wittig reaction.

Ma and co-workers performed a NHC-catalyzed **122** annulation reaction between β -halovinyl aldehydes **6**, **11** and



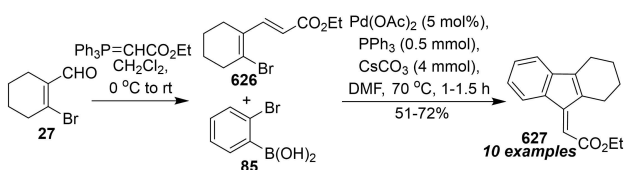
Scheme 175. Synthesis of MBH adducts and their bromination.



Scheme 176. Synthesis of new type of aza-Baylis–Hillman adducts.

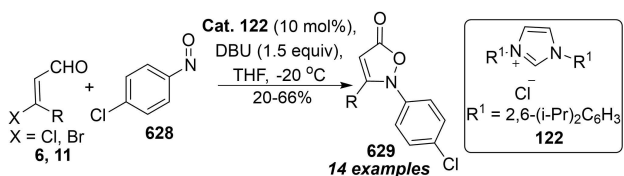


Scheme 177. Mechanism for the synthesis of quinoline ring.

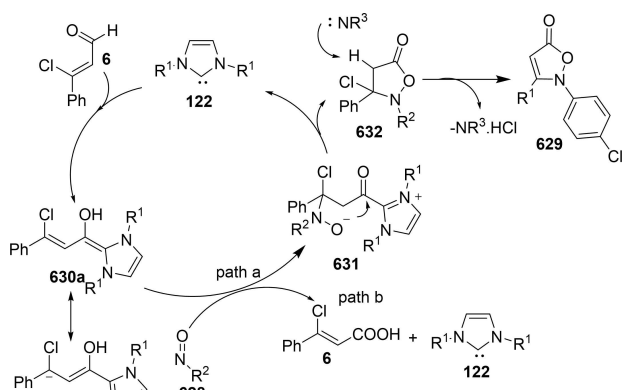


Scheme 178. Preparation of fluorenylidene derivatives via Pd-catalyzed intramolecular Suzuki reaction followed by Heck coupling.

nitrosobenzenes **628** under milder reaction conditions, to obtain 2,3-disubstituted isoxazol-5(2*H*)-one derivatives **629** (Scheme 179).^[147] A plausible mechanism for this metal-free



Scheme 179. NHC catalyzed synthesis of 2,3-disubstituted isoxazol-5(2*H*)-one derivatives via 3 + 2 annulation.



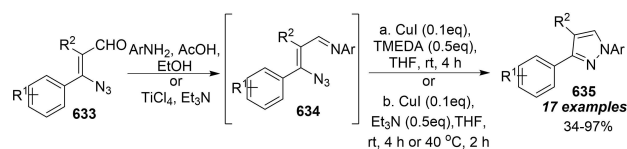
Scheme 180. Probable reaction mechanism of the NHC-catalyzed annulations.

approach to afford isoxazol-5(2*H*)-one derivatives is presented as Scheme 180.

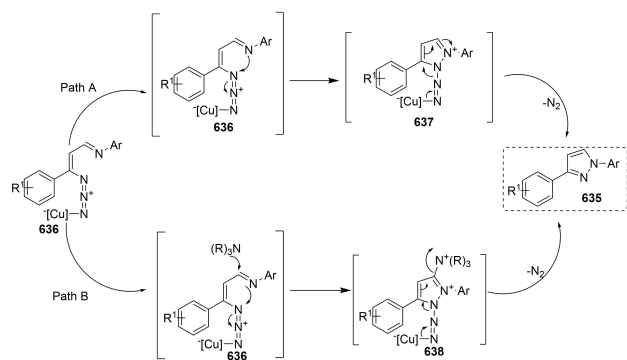
Rao and co-workers explored β -halovinyl aldehydes **6** and discovered a facile and efficient copper-catalyzed intramolecular amination strategy to provide an easy access to diverse range of multi-substituted 1*H*-pyrazoles **635** under milder reaction conditions (Scheme 181).^[148] The synthesis of 1*H*-pyrazoles **635** was achieved via Cu-catalysed cascade annulation of β -azido imines **634** which were in turn prepared via condensation of β -azidovinyl aldehydes **6** and substituted anilines. Using this protocol, the authors synthesized a highly selective ligand for estrogen receptor in three steps, mechanism has been depicted in Scheme 182.

In an extension to their previous findings, Ray group demonstrated an unorthodox and effective Pd-catalyzed method for synthesizing cyclopentenone derivatives **607** and cyclopentanols via intramolecular oxidative cyclization of substituted homoallylic alcohol derivatives **640** (Scheme 183).^[149] This method was found to have practical applications for the synthesis of sesquiterpenes. Mechanism of cyclization and the key step of the tandem reaction, were verified by density functional theory calculations (Scheme 184).

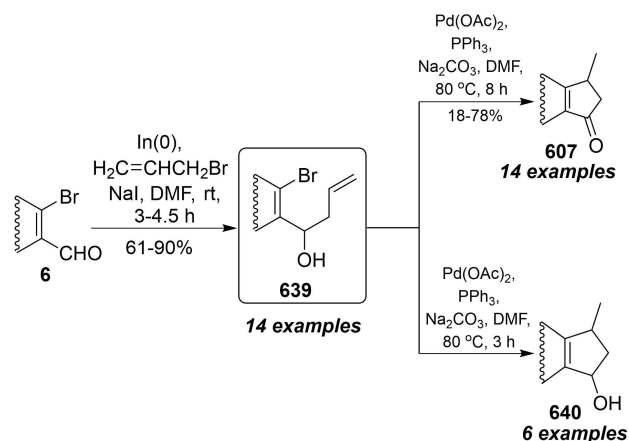
Venkatesan and co-workers designed and synthesized highly effective phosphorescent emitter boron compounds **646** (Scheme 185).^[150] To customize the phosphorescence emission properties in neat, solid, solution, and in doped PMMA thin films, a combination of proper molecular frameworks and appropriate electronic nature of the substituents were employed. The synthesis was achieved by reacting β -halovinyl aldehydes **27** with *p*-nitroaniline **125** in presence of *p*-TSA and H₂O which led to formation of Schiff base as well as hydroxylation of β -halogen. Further reaction with BF₃·OEt₂



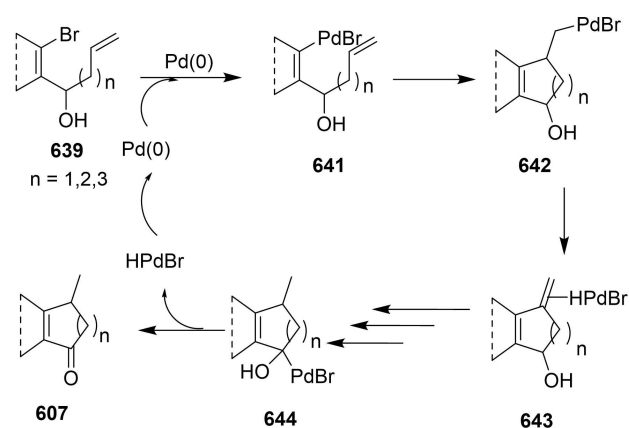
Scheme 181. Cu-catalyzed intramolecular amination reaction for synthesizing 1*H*-pyrazole derivatives.



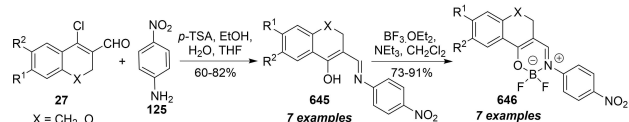
Scheme 182. Proposed mechanistic pathway for the formation of pyrazole derivatives.



Scheme 183. Pd-catalyzed synthesis of substituted cyclopentenone derivatives.



Scheme 184. Mechanistic pathway for the synthesis of cyclopentenone derivatives.

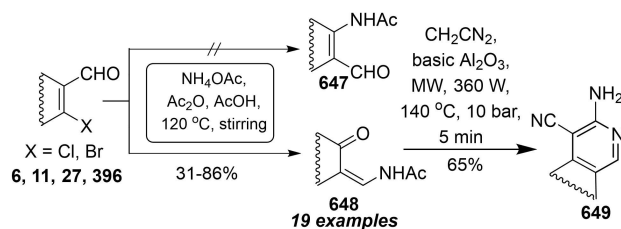


Scheme 185. Synthesis of boron compounds from hydroxyvinylimines.

resulted in formation of phosphorescent emitter boron compounds **646**.

Boruah group prepared a library of steroidal and non-steroidal (*Z*)- β -ketoenamide derivatives **648** from β -halovinyl aldehydes **6**, **11**, **27**, **396** (Scheme 186).^[151] One of the synthesized β -keto-enamide derivatives **648** was also transformed into 2-amino-dihydroisoquinoline **649** via condensation with malonitrile under MW irradiation in presence of alumina. Single crystal XRD studies were carried out to confirmation the structures of the products as β -keto-enamide **648** and not **647**.

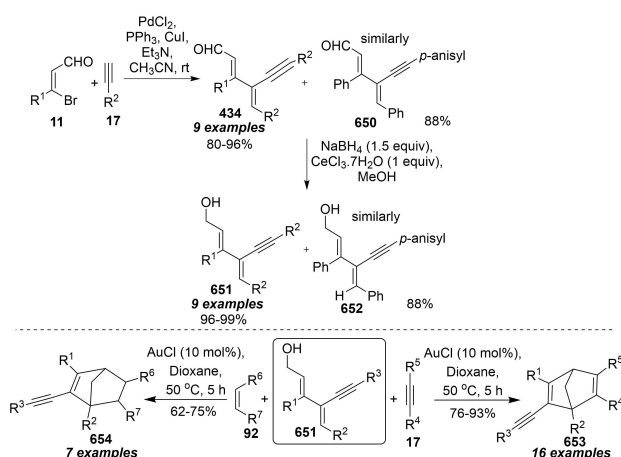
Swamy group carried out a Au(I)-catalysed one-pot dehydrative cyclization of alkynyldienols **651** into cyclopentadiene **659** which upon intermolecular [4 + 2] cycloaddition with activated alkynes/alkenes **17**, **92** yielded the highly substituted



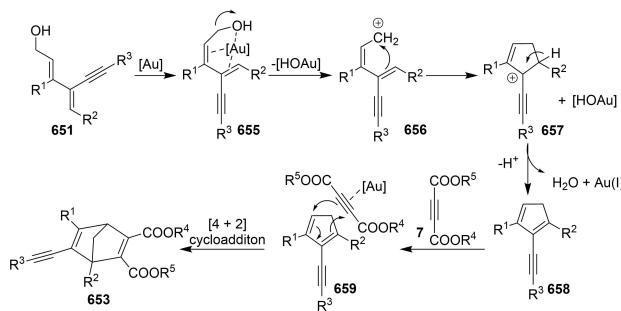
Scheme 186. Synthesis of β -ketoenamides from β -halovinyl aldehydes.

norbornadiene/norbornene derivatives **653–654** (Scheme 187).^[152] The precursors like alkynyldienols **651**, were obtained through sequential Sonogashira cross-coupling of β -bromovinyl aldehydes **11** and alkynes **17** followed by Luche reduction. The enynals **434** and multisubstituted norbornadiene derivatives **653–654** were synthesized in 62–96% yields. Mechanism for the formation of norbornadiene/norbornenes is presented in Scheme 188.

Tang group reported a regioselective and operationally straightforward [3 + 2] annulation reaction of β -chlorovinyl dithianes **77** and α,β -unsaturated carbonyl compounds **660**. This procedure provided the direct approach to highly functionalized cyclopentene derivatives **661–662** with excellent regio- and chemoselectivity under milder reaction conditions. An



Scheme 187. Au(I)-catalysed synthesis of norbornadiene and norbornene derivatives.



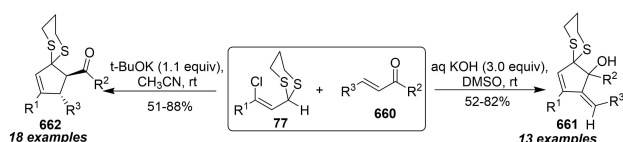
Scheme 188. Probable pathway for the synthesis of norbornadienes/norbornene.

unusual cyclization selectively afforded the hydroxylated cyclopentene derivatives **661** (Scheme 189).^[153]

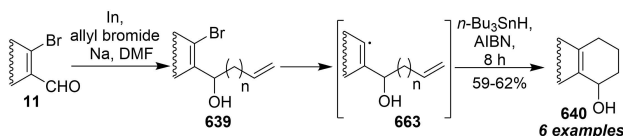
Chaudhuri and co-workers reported tri-*n*-butyltin hydride (TBTH) catalysed synthesis of hydroxycyclohexene fused carbocycles **640** by using 6-bromo-hepta-1,5-diene-4-ols **639** as an intermediate, and azobisisobutyronitrile (AIBN) as an initiator under refluxing condition in benzene (Scheme 190).^[154]

Ray and co-workers described a simple and convenient approach for the synthesis of substituted cycloheptenone derivatives **664** from 1-bromo octa-1,7-diene-3-ol derivatives **639** which were in turn prepared via reaction of β -bromovinyl aldehydes **11**, **27** with Grignard reagent **605** (Scheme 191).^[155] This reaction proceeds via intramolecular 7-*exo-trig* cyclization under Pd(0) catalyzed conditions which then followed Pd(II)-catalyzed oxidation of hydroxyl functionality. DFT calculations were taken into account for evaluating the reaction pathway.

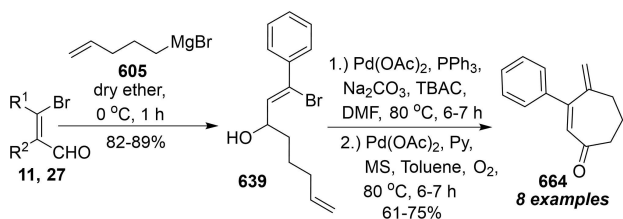
Talukdar group developed a copper-catalyzed efficient protocol for the synthesis of acyclic as well as cyclic amidine derivatives **667–669** via reaction of enynamines **665** with sulfonylazide derivatives **666** (Scheme 192).^[156] It was proposed that enynamines **665** generated a cycloadduct **670** which upon



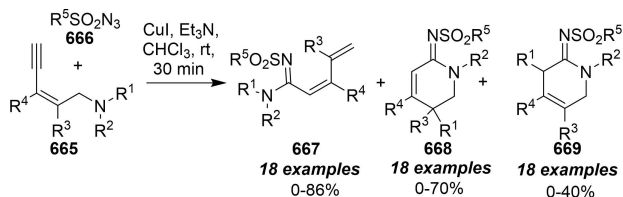
Scheme 189. Synthesis of highly functionalized hydroxylated cyclopentenones via [3 + 2] cyclization reaction.



Scheme 190. Synthesis of hydroxycyclohexene fused carbocycles.



Scheme 191. Synthesis of cycloheptenone derivatives.



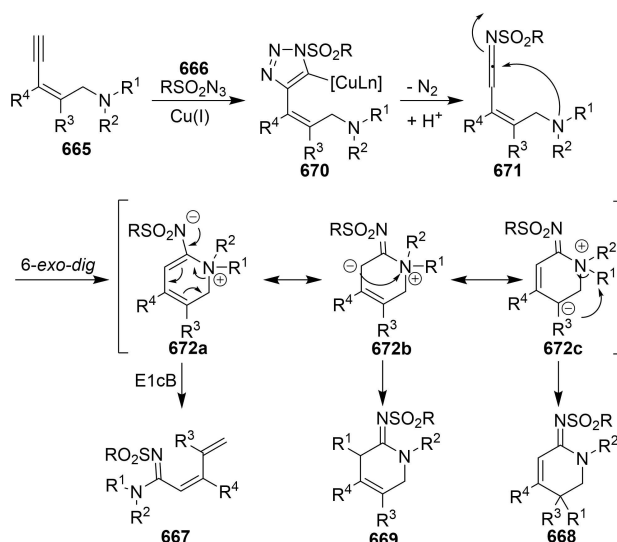
Scheme 192. Cu(I) catalyzed synthesis of acyclic and cyclic amidine derivatives.

loss of N₂ yielded a ketenimine **692** and nucleophilic intramolecular 6-*exo-dig* attack furnished a six-membered cyclic zwitter ionic intermediate **672** which further facilitated migration of the tethered amino group to the C₅- center producing an acyclic amidine **667**. At the same time, migration of a substituent on the amino group to C₂- and C₄-centers resulted in the synthesis of cyclic amidine derivatives **668–669** (Scheme 193). To understand the mechanism, computational studies were performed which indicated that the product distribution was dependant on the substitutions over the enynamine backbone **665**.

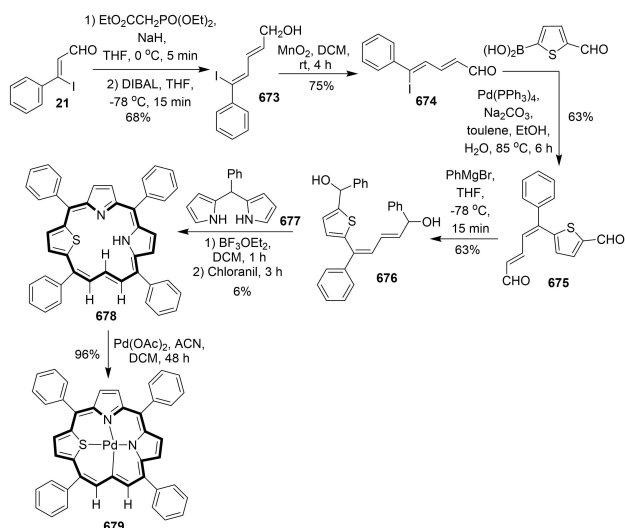
Allyliporphyrin is a carboxyporphyrin in which one pyrrole ring has been replaced by an allyl group. Cho and co-workers synthesized Allyliporphyrin using β -iodovinyl aldehydes and studied the bond rotation by variable temperature and DFT calculations. The bond rotation was first observed in the limited space of the carboxyporphyrin from **678** through *cis*-**678** and the calculated rotational barrier was low enough, with the relative energy level of *cis*-**678** only 0.65 kcal/mol higher than **678**. Chemical shifts of the inner NH and CH signals confirmed that the synthesized allyliporphyrin **678** is a strongly aromatic macrocycle. The palladium complex of allyliporphyrin exhibited reduced aromaticity because of the tilted thiophene of Pd-**678** (or simply **679**) (Scheme 194).^[157]

Yang group developed two isomeric dioxabicyclic molecular skeletons by using the divergent synthesis concept. A pseudo-three-component reaction using two equivalents of 4-hydroxycoumarin **58** and (*Z*)- β -chlorovinyl aldehyde **2** furnished the corresponding bis(4-oxycoumarin)-based 2,6- and 2,8- dioxabicycles **680**, **681** respectively, under acid-catalyzed conditions and using a base (Scheme 195).^[158] The obtained colorless 2,6-dioxabicycles upon UV irradiation turned red and when exposed to visible light a reverse reaction proceeded. It was proposed that photochromism proceed through a sequential [4 + 4]-(heterocyclo)addition/reversion and 1,5-hydrogen shift.

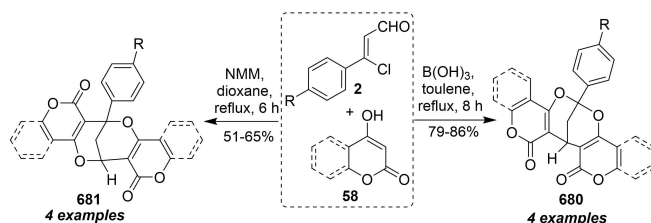
Joshi and co-workers presented a direct amidation reaction of ferrocenyl/phenyl substituted β -chlorovinyl aldehydes **6**, **74**



Scheme 193. Mechanism for the synthesis of amidine derivatives.

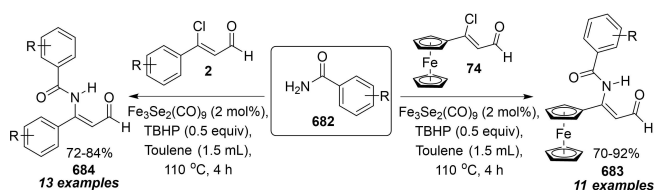


Scheme 194. Synthesis of allylporphyrin and its Pd(II) complex.

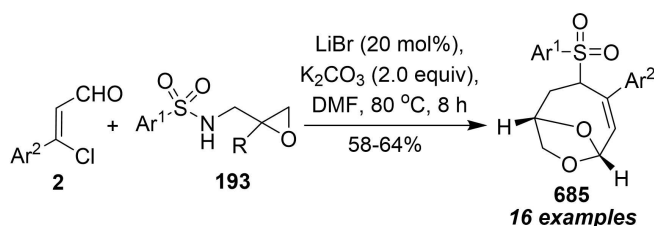


Scheme 195. Pseudo-three-component synthesis of dioxabicycles.

in presence of a chalcogen stabilized iron selenide carbonyl cluster $\text{Fe}_3\text{Se}_2(\text{CO})_9$. Reaction was found to exhibit a wide substrate scope for functionally different amides **682** and β -chlorovinyl aldehydes **2**, **74**. Furthermore, it was found that 2 mol % of $\text{Fe}_3\text{Se}_2(\text{CO})_9$ cluster was extremely effective to couple diversely substituted primary amides (whether hetero, aliphatic, aromatic) with β -chlorovinyl aldehydes **2**, **74** under aerobic



Scheme 196. Amidation of β -chloro-ferrocenyl aldehydes under Fe-carbonyl chalcogen cluster catalysis.



Scheme 197. Formation of dioxo-3-azabicyclonone-4-ene motifs.

conditions within 4 h. This was the first report in which direct amidation reaction was carried out to obtain α,β -unsaturated derivatives (Scheme 196).^[159]

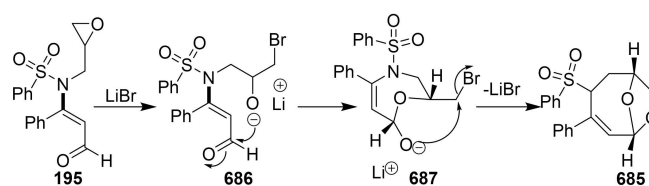
Swamy and co-workers developed an elegant approach for the synthesis of unorthodox dioxo-3-azabicyclonone-4-ene motifs **685** by carrying out a transition metal-free reaction between N-oxiranylmethyl benzenesulfonamide **193** and β -chlorovinyl aldehyde **6**, using LiBr/ K_2CO_3 in DMF as the reaction medium (Scheme 197). The synthesis of dioxo-3-azabicyclonone-4-ene motifs **685** was realised through ring expansion reactions (Scheme 198).^[151]

Our group also prepared two series of benzenesulfonamide derivatives having thioureido-linked pyrazole **691** and amino-1,2,4-thiadiazoles **692** using β -chlorovinyl aldehydes **6** as the precursor. These benzenesulfonamide derivatives were investigated as human carbonic anhydrase (hCA) inhibitors against isoforms I and II along with the tumor-associated isoforms IX and XII. Molecular modeling studies against isoforms hCA I, II, and XII of some selected derivatives were also carried out. This report provided an unorthodox strategy for synthesizing amino-1,2,4-thiadiazole derivatives **692** using 3-amino isoxazole **689** derivatives and 4-isothiocyanatobenzenesulfonamide **690** as reactants. It was revealed that amino-linked 1,2,4-thiadiazoles **692** were found to be better inhibitors of the cytosolic isoform, hCA I, in comparison to thioureido-linked pyrazoles **691** (Scheme 199).^[160]

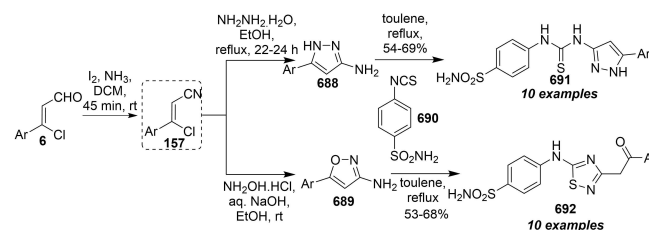
It is mentioned that a brief summary of various heterocycles generated during 2007–2024 are highlighted in Schemes 200 and 201.

8. Summary and Outlook

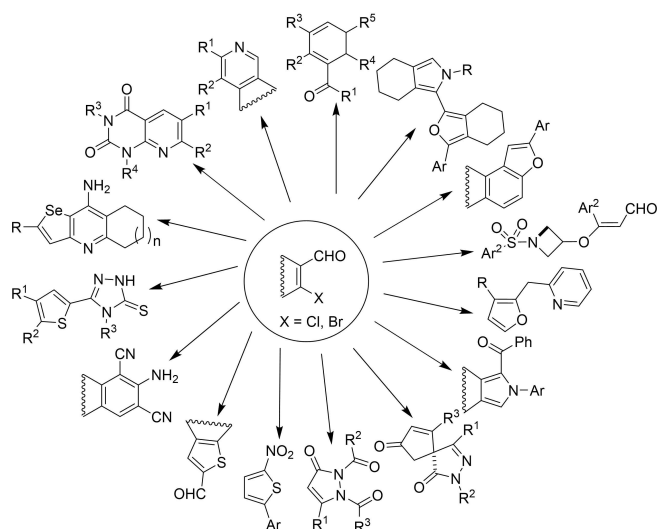
On the basis of previous findings, it can be concluded that β -halovinyl aldehydes holds an important place in the field of organic synthesis and have been used for the synthesis of



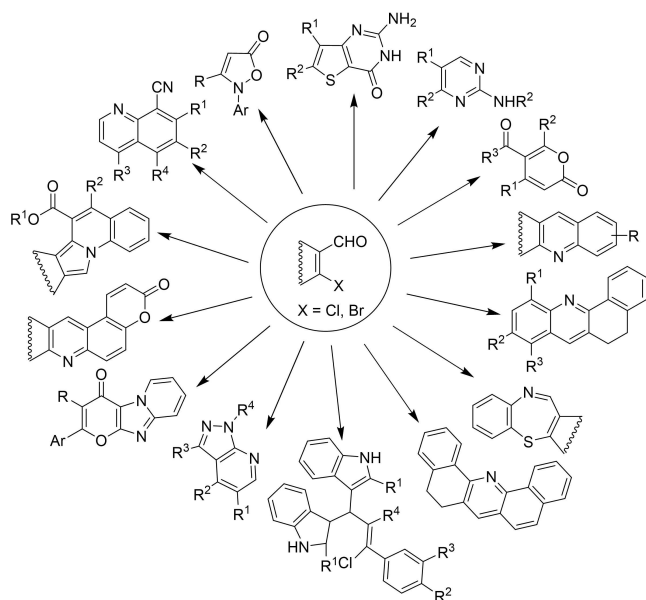
Scheme 198. Mechanism for the formation of dioxo-3-azabicyclonone-4-enes.



Scheme 199. Synthesis of the benzenesulfonamides containing thioureido-linked pyrazoles and amino-1,2,4-thiadiazoles.

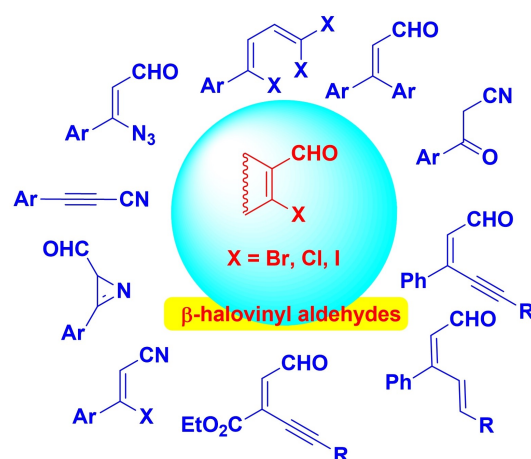


Scheme 200. An overview of various heterocycles generated during the time interval of mid-2007 to Jan 2024.



Scheme 201. An overview of various heterocycles generated during mid-2007 to Jan 2024.

various privileged heterocycles and other cyclic frameworks which are not reported in literature or deemed difficult to synthesize. β -halovinyl aldehydes have emerged as important building block for synthesizing different kind of heterocycles including monocyclic, bicyclic, macrocycles and spiro heterocycles. In fact, β -halovinyl aldehydes serve as important aldo-X bifunctional building block (AXB3 s) due to the presence of two most explored electrophilic reactive functionalities (formyl group and benzylic halogen) in organic synthesis. More importantly, these two reactive sites are in close proximity to each other and that is why it readily reacts with diverse bifunctional nucleophiles to furnish cyclic frameworks through tandem reactions. It was observed that halogen group of



Scheme 202. An overview of future scope of this building block.

halovinyl aldehyde behaves more like a benzylic halogen and less as vinylic halogens and sometimes it is electrophilically more reactive than the formyl group and chemoselective nucleophilic substitution reaction is preferred over condensation reaction though this is not true for some cases and it all depends on reaction conditions. A variety of aza-, oxa-, thio- and carbonucleophiles readily react with β -halovinyl aldehydes and a variety of heterocycles have been developed including azirine, pyrrole, furan, thiophene, pyrazole, oxazole, isoxazole, triazole, thiadiazole, oxadiazole, pyridine, pyrimidine, quinoline, isoquinoline, acridine and other macrocycles like allylporphyrin. Also several carbocycles like benzene derivatives, cyclopentene, cyclohexene, cycloheptene, norbornadiene, and norbornene have been prepared. The alkenic moiety of β -halovinyl aldehydes also makes them suitable substrate for Diel-Alder reactions. Several new strategies have been discovered so far and in the near future many more advancements and achievements are expected to be coming from β -halovinyl aldehydes. The future scope is anticipated to be lying with exploration of new building blocks e.g. propynitriles, *o*-enyl aldehydes, β -keto nitriles, β -azidovinyl aldehydes, aziridine aldehydes etc. (Scheme 202) which could be readily accessed in a single operation from β -halovinyl aldehydes.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: β -chlorovinyl aldehydes • Vilsmeier-Haack reaction • Sonogashira coupling • Aldo-X bifunctional building block (AXB3 s) • Cascade reaction

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